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NITROGENOUS FIVE-MEMBERED RING COMPOUNDS (54)

(57) The present invention is to provide an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [1] .

$$\mathbb{R}^{2}$$
-X-B \mathbb{N}^{1} $\mathbb{N}^$

wherein symbols in the formula have the following meanings:

A: -CH2- or -S-, B: CH or N,

R1: H, a lower alkyl group, etc.,

X. a single bonding arm, -CO-, -Alk-CO-, -COCH₂-, -Alk-O-, -O-CH₂-, -SO₂-, -S-, -COO-, -CON(R²)-,

-Alk-CON(R³)-, -CON(R³)CH $_2$ -, -NHCH $_2$ -, etc., R³: hydrogen atom or a lower alkyl group, Alk: a lower alkylene group, and

R2: (1) a cyclic group which may be substituted, (2) a substituted amino group, etc.,

provided that when X is -CO-, then B is N, or a pharmaceutically acceptable salt thereof.

Description

TECHNICAL FIELD

[0001] The present invention relates to a novel nitrogen-containing 5-membered ring compound having superior dipeptidylpeptidase IV (DPPIV) inhibitory action that is useful as a charmaceutical.

BACKGROUND ART

- 0 [0002] Dipeptidylosptidase IV (DPPIV) is a kind of serine protease that specifically hydrolyzes a dipeptide of Xaa-Pro or Xaa-Ala (where Xaa may be any amino acid) from the N terminus of a polypeptide chain.
 - [0003] There are various reports regarding the role of DPPIV (also called to as CD28) in the body and its relationship, with diseases (rich; et al., Current Mediceles vol. 47, pp. 1863-1970, 1998). Aquaystrys, et al., Current Mediceles vol. 47, pp. 1863-1970, 1998). Aquaystrys, et al., Current Mediceles vol. 47, pp. 481-491. Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol. 20, pp. 367-375, 1999;
 - [0004] GLP-1 (glucagon-like peptide 1) is a peptide hormone that mainty acts in the pancreas after being secreted from the lower small intestine after meals, and primarily has the function of amplifying glucoso-induced insulin secretion. In addition, there are several reports suggesting that GLP-1 has an appetite-suppressing action. DPPIV hydrolyzes GLP-1, forming an inactive or antagonistic poptide.
- 20 [0005] Substances that inhibit the enzyme activity of DPPIV enhance the insulin secretion response to oral glucose loading by enhancing the action of intrinsic GLP-1, thereby improving impaired glucose tolerance.
 - [0006] Consecuently, DPPIV Inhibitors are considered to be useful for the prophylaxis and treatment of diabetes (particularly type 2 diabetes), etc. Also, they are expected to be effective for the prophylaxis and treatment of other diseases induced or exacerbated by impaired glucose tolerance (including hyperglycemia (such as postprandial hyperglycemia), hyperinsulinemia, diabetes complications (such as renal disorder and neurological disorder), ligid me-
- tabolism disorder and obesity, etc.).

 [0007] Moreover, DPPIV inhibitors are also expected to be effective for the prophylaxis and treatment of diseases
 - hat are to be improved by enhancing the appoilte-suppressing action of GLP-1 (including overcating and obssity, etc.).

 [0008] Also, DPPV (CD26) preent on the surface of T cells is strongly upregulated following T cell activation, and plays an important role in the activation and proliferation of T cells, T cell activity is known to be suppressed when DPPIV (CD26) is blocked by antibodies or inhibitory substances. Also, there has been an interest in the correlation between this enzyme and the pathological state in collagen metabolism disorders and diseases associated with abnormal immunity. For example, the DPPIV (CD26) positive rate of peripheral blood T cells is elevated in meumatoid patients, and high levels of DPPIV activity have been detected in the urine of nephritis patients. Moreover, DPPIV (CD26) is also thought to play an important role in the entry of HIV into Immorporeyes.
 - [0009] Consequently, substances that inhibit DPPIV (CD28) are expected to demonstrate prophylactic and therapeutic effects against diseases including autoimmune diseases (such as arthritis and rheumatoid arthritis), osteoporosis, acquired immunodeficiency syndrome (AIDS) and relections of transpointed orans and tissues.
- [0010] On the other hand, as compounds having DPPIV inhibitory action, there are described 2-cyanopyrrolidine devalves having DPPIV inhibitory action in International Patent Laid-Open Publications Nos. WO98/1998 and WO0074241.
 - [0011] The present invention provides a novel aliphatic nitrogen-containing 5-membered ring compound having an excellent DPPIV inhibitory action.
- [0012] As a result of earnest research to solve the above problems, the present inventors found a novel nitrogencontaining 5-membered ring compound having DPPIV inhibitory action, thereby accomplished the present invention.

DISCLOSURE OF THE INVENTION

[0013] Namely, the present invention relates to an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [i]:

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$$R^{2}$$
-X-B NH-CH₂-CO-N A [I]

10 wherein symbols in the formula have the following meanings:

A: -CH2- pr -S-,

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B; CH or N,

D. OITOIN,

R1: H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X: a single bonding arm, -CO-, -Alk-CO-, -COCH₂-, -Alk-O-, -O-CH₂-, -SO₂-, -S-, -COO-, -CON(R³)-, -Alk-CON(R³)-, -CON(R³)-, -CON(R³)-, -SO₂N(R³)- or -NHCH₂-,

where the bonding arm at a right terminal in each definition of the above X represents a bonding arm with B,

R3: hydrogen atom or a lower alkyl group,

Alk: a lower alkylene group, and

R2: a group selected from the following (1), (2) and (3):

- (1) a cyclic group which may be substituted, where the cyclic group portion is
 - (i) a monocyclic or bicyclic hydrocarbon group, or
 - (ii) a monocyclic or bicyclic heterocyclic group;

(2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from a substituted or unsubstituted lower alkyl group; and

(3) a lower alkryl group, a carboxy lower alkryl group, a lower alkoxy group, a lower alkenyl group, a lower alkoxysubstituted lower alkyl group, a phenoxy group, a phenoxy-substituted lower alkyl group or a phenyl lower alkenyl group,

35 provided that when X is a single bonding arm, then R² is a group selected from the above (1) and (2), and when X is -CO-, then B is N, or a pharmaceutically acceptable salt thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0014] Although optical isomers based on an asymmetric carbon can be present in the objective compound [1] of the present invention, the present invention includes any of these optical isomers as well as mixtures thereof. In addition, although isomers (cls form or trans form) are also present based on the relative positions of substituents with respect to the standard plane of a cyclic group, the present invention also includes any of these isomers as well as mixtures thereof

5 [0015] In the present invention, examples of a lower alkyl group, a lower alkylthio group, a lower alkylsuifonyl group, a lower alkylsuifonyl group a lower alkylsuifonyl group and a lower alkylsuifonyl group include linear or branched groups having 1 to 6 carbon atoms, and particularly those having 1 to 4 carbon atoms.

10016] Also, examples of a lower alkianoyl group and a lower alkanoylamino group include linear or branched groups having 2 to 7 carbon atoms, and particularly those having 2 to 5 carbon atoms. Examples of a lower cyclosikery group and lower cyclosikery group include those having 3 to 8 carbon atoms, and particularly 3 to 6 carbon atoms. Examples of a lower alkylene group include linear or. branched groups having 1 to 6 carbon atoms, and particularly 1 to 4 carbon atoms. Examples of a lower alkivyleng or group include linear or. branched groups having 1 to 6 carbon atoms, and particularly 1 to 4 carbon atoms. Examples of a lower alkivyl group and lower alkivyleng group include those having 2 to 7 carbon atoms, and particularly 2 to 5 carbon atoms. Moreover, examples of a halegon atom include fluorine, chlorine, bromine and iodine. [0017] in the compound [I] of the present invention, specific examples of "hydrogen atom, a lower alkyl group, a hydroxyl lower alkyl group or lower alkyl group. Hower alkyl group is decreased by 1 include hydrogen atom, methly group, hydroxymethyl group, methoxymethyl group, etc. Among them, hydrogen atom or a lower alkyl group (such as methyl group, etc.) a preferred.

[0018] In the compound [i] of the present invention, a cyclic group portion of "a cyclic group which may be substituted"

represented by R2 includes

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- a monocyclic or bicyclic hydrocarbon group and
 a monocyclic or bicyclic heterocyclic group.
- [0019] Such monocyclic or bicyclic hydrocarbon groups include those having 3 to 15 carbon atoms, which may be partially or completely saturated.
- [0020] As the monocyclic hydrocarbon group, those having 3 to 7 carbon atoms are preferred, examples of which may include pheny; group, cyclohoxyl group, cyclopontyl group, cyclobutyl group, cyclopropyl group, and partially or
- completely saturated cyclic groups thereof, etc. [0021] As the bicyclic hydrocarbon group, those having 9 to 11 carbon atoms are preferred, examples of which may include an Indanyi group, an Indonyi group, a nephthyl group, a tetrahydronaphthyl group and partially or completally saturated oxyclic groups thereof, etc.
- [0022] Examples of the monocyclic or bicyclic heterocyclic groups may include a monocyclic or bicyclic heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which may be partially, or completely saturated.
 - [0023] Examples of the monocyclic heterocyclic groups may include a heterocyclic group containing 1 to 2 hetero atoms selected from hitrogen atom, oxygen atom and sulfur atom and comprising of a saturated or unsaturated 5-to 7-membered ring, and specifically mentioned are: a pyrrolidingly group, an imidazolighting group, a pyrazolidinyl group, an oxolianyl group, a thiracybly group, an imidazolinyl group, a pyrazolid group, a thiracybly group, a pyrazolid group, a thiracybly group, a pyrazolyl group, a thiracybly group, a pyrazolyl group, a thiracybly group, a pyrazolyl group, a pyrazolyl group, a thiracybly group, a pyrazolyl group, a gyrazolyl g
- and partially or completely saturated cyclic groups thereof, etc.
- [0024] Examples of the bicyclic heterocyclic group may include a heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two saturated or unsaturated 5- to 7-membered rings being fused, and specifically mentioned are an indicinity group, an isolindicity group, a nindoxy group, an indiversity group, a high group, a high group, a henzonization group, a benzonization group, a benzonization group, a benzonization group, a tenzonization group, a denzonization group, a disposity group, and group, and
- 35 [0025] Among these cyclic groups (monocyclic or bicyclic hydrocarbon groups or monocyclic or bicyclic heterocyclic groups).
 - "(f) a monocyclic hydrocarbon group having 3 to 7 carbon atoms,
 - (ii) a monocyclic heterocyclic group (preferably, a monocyclic 5- to 6-membered aliphatic heterocyclic group) containing 1 to 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or
 - (III) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused"
- is preferred, and examples of which may include:
- 4º "phony group, cyclohexyl group, cyclopontyl group, cyclobutyl group, cyclopropyl group, a pyrrolidinyl group, an imidazolifyl group, an oxolanyl group, a thiolanyl group, a pyrrolidinyl group, an imidazolifyl group, an oxolanyl group, a thiolanyl group, a thiolanyl group, a midazolifyl group, a pyrazolyl group, a thiolazolyl group, a pyrazolyl group, a bonzolyl group, a pyrazolyl group, a pyrazolyl group, a pyrazolyl group, a bonzolyl group, a chinazolyl group, a chinazolyl group, a pyrazolyl group, a chinazolyl group, a pyrazolyl group, a
 - [0026] Among them, "(i) a monocyclic heterocyclic group . (preferably, a monocyclic 5- to 6-membered alliphatic heterocyclic group) containing 1 to 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or (ii)

a bloydlicheterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused" is more proferred.

[0027] Also, among them, more preferred examples may include:

*phoryl group, cyclohexyl group, cyclopronyl group, a pyrrolidinyl group, an irridazolidinyl group, a pyrrazolidinyl group, a pyrrazolidinyl group, a pyrrazolidinyl group, a myrazolidinyl group, a myrolyl group, an isoxacolyl group, a myropholinyl group, a pyrrazolidinyl group, a pyrrazolidinyl group, a myrazolidyl group, a pyrrazolidyl group, a pyrazolidyl group, a myrazolidyl gro

and partially or completely saturated cyclic groups thereof, etc."

[0028] Also, more preferred examples may include: "a toperdyl group (1-piperdyl group, etc.), a piperazinyl group

(1-piperazinyl group, etc.), a morpholinyl group (4-morpholinyl group, etc.), an indolinyl group, etc.), etc."

an isoindolinyl group (2-isoindolinyl group, etc.), at hitazolopyridyl group (thiazolof)4-bjoyridin-2-yl group, etc.), etc."

[0029] Also, among them, particularly preferred examples may include:

"1-piperidyl group, 1-piperazinyl, group, 4-morpholinyl group, 1-indolinyl group, 2-isoindolinyl group, thiazolo-[5,4-b] pyridin-2-yl group, etc.".

[0030] "A cyclic group (a monocyclic or bicyclic hydrocarbon group or a monocyclic or bicyclic heterocyclic group) which may be substituted" represented by R2 may be unsubstituted or may have 1 to 3 substituents which are the same or different.

[0031] The substituent(s) of the cyclic group is/are not particularly limited, and examples of which may include substituents selected from the following "substituents of Group A". Among them, "substituents of Group A" are more preferred.

[0032] In the objective compound [] of the present invention, substituents of "the armino group substituted by 1 or 2 substituents which are the same or different, selected from a substituted or unsubstituted lower airty group" represented by PR are not particularly immited, and exemples of which may include a lower airty group substituted by a group selected from "cyano group, a lower allowy group (methoxy group, etc.), a monopyclic anyl group (phenyl group, etc.), a nitrogen-containing monocyclic 6-methored aromatic heterocyclic group (a portify droup, etc.), an itrogen-containing monocyclic 6-methored aromatic heterocyclic group (a portify) group, etc.), and the production of the prod

- - - Substituents of Group A: - - - - -

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[0033] As substituents of Group A, the following substituents are exemplified:

a halogen atom (CI. F, Br, etc.), cyano group, nitro group, amino group, oxo group, a lower alkyl group, a lower alkoxy group, a halo-lower alkyl group, a lower alkoxybarbonyl group, a lower alkoxybarbonylamino group, a labo-lower alkyl group, a halo-lower alkyl-barbonyl group, a halo-lower alkyl-barbonylamino group, a monocyclic group, a monocyclic group, a monocyclic group, a monocyclic group alkyl-barbonylamino group, a lower alkyl

(As "a nitrogen-containing monocyclic 5- to 6-membered aliphatic heterocyclic group" in "the nitrogen-containing monocyclic 5- to 6-membered aliphatic heterocyclic group-substituted carbonyl group", specific exemples include "a pyrrolidinyl group, a piperdinyl group, e.g.

[0034] Also, as "the nitrogen-containing monocyclic 6-membered aromatic heterocyclic group", specific examples may include "a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a p

[0035] As "the monocyclic aryl group" portion in "the monocyclic aryl group" and "the monocyclic aryl group-substituted aryl lower alkylcarbonylamino group", specific examples may include phonyl group, etc.)

- - - Substituents of Group A' (particularly preferred substituents of Group A):-----

[0036] As more preferred substituents of Group A, the following substitutes are exemplified:

oxo group, a lower alkanoyl group, a lower cycloalkanoyl group, a lower alkoxycarbonyl group and a nitrogen-containing monocyclic 5-to 5-membered aliphalic heterocyclic group-substituted carbonyl group (a pyrrolidinyl group, a piperidinyl group, a poperidinyl group, a pyrolidinyl group and a nitrogen-containing monocyclic group and a nitrogen-containing

[0037] Among the objective compounds [1] of the present invention wherein B is CH, in case that X is a single bonding arm, preferred examples for R² my include (1) a monocyclic or buyelin Enrogen-containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substituents selected from a substituted or unsubstituted lower allow 'aroup, ceresented by the formula:

[0038] In the objective compound [I] of the present invention wherein B is CH, among the two kinds of distrians isomers based on a cyclohexyl ring in the structure [II] as a standard plane, a transisomeric compound is more preferred from the viewpoint of obtaining a higher DPPIV inhibitory activity. That is, among the objective compound [I] of the present invention wherein B is CH, a compound having the following partial structure.

or a pharmaceutically acceptable salt thereof is preferred.

[0039] As one compound group of the compounds of the present invention, among the compounds of [i], those wherein X is a single bonding arm, Alk-CO, -COCH₂, -Alk-CO, -C-CH₂, -S-C₂, -S, -COC, -CON(R³)-, -Alk-CON(R³)-OH₂, -COCH₂, -COCH₂, -COCH₂, -COCH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -COCH₂, -COCH₂, -COCH₂, -S-C₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -Alk-CON(R³)-OH₂, -COCH₂, -Alk-CON(R³)-OH₂, -Alk-CON(R³)-OH₂-Alk-CON(R³)-OH₂-Alk-CON(R³)-OH₂-Alk-CON(R³)-OH₂-Alk-CON(R³)-OH₂-Alk-CO

(f) a monocyclic or bicyclic hydrocarbon group, or

(ii) a monocyclic or bicyclic heterocyclic group; or (2) an amino group substituted by 1 or 2 substituents which are
the same or different and selected from a substituted or unsubstituted lower alkyl group, can be exemplified.

(Compound Group 1, Compound I-e)

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[0040] Also, as other compounds group, among the compounds

- [i] or the above-mentioned Compound Group 1, compounds group in which R² is a group selected from (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A, where the cyclic group portion is (i) a monocyclic or bicyclic hydrocarbon group, or (ii) a monocyclic or bicyclic hydrocarbon group, or (iii) a monocyclic or bicyclic hy
- (2) an amino group substituted by 1 to 2 substituents which are the same or different and selected from 1a lower alkyl group which may be substituted by a substituent selected from cyano group, a lower alkoxy group, phonyl group and a nitrogen-containing monocyclic 6-membered aromatic heterocyclic group*; and
 - (3) a lower alkyl group, a carboxy lower alkyl group, a lower alkoxy group, a lower alkonyl group, a lower alkoxy-substituted lower alkyl group, phenoxy group, a phenoxy-substituted lower alkyl group or a phenyl lower alkenyl group.

may be exemplified (Compound Group 2).

[0041] Also, as another compounds group, among the compounds

- [i] or the above-montioned Compound Group 1 or 2, compounds group in which R² is a cyclic group which may be substituted, where the cyclic group portion is a group selected from
 - a monocyclic hydrocarbon group having 3 to 7 carbon atoms.
 - (ii) a monocyclic heterocyclic group containing 1 to 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and
 - (iii) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused may be exemplified (Compound Group 3).

[0042] Also, as another more preferred compound group, among the compounds [I] or the above-mentioned Compound Group 1, 2 or 3, compounds in which R² is a cyclic group which may have 1 to 3 substituents which are the same or different, selected from the substituents of Group A', where the cyclic portion is a group selected from a piperfely group, a piperszlinyi group, a morpholinyi group, an indolinyi group, an isolndolinyi group, and a thiazolopyricyi group may be exemplified (Compound Group 4).

[0043] Also, as another preferred compound group, among the compounds [i] or the above-mentioned Compound

Group 1, 2, 3 or 4, compounds wherein B is CH, X is a single bonding arm and R² is (1) a monocyclic or bjcyclic nitrogen containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substituents selected from a substituted or unsubstituted flower alley group, represented by the formula:

$$N-$$

may be' exemplified (Compound Group 5).

[0044] Also, as another preferred compound group, among the compounds [I] or the above-mentioned Compound Group 1, 2, 3, 4 or 5; compounds group wherein B is CH, X is a single bonding arm, and A is -CH₂-; compounds group wherein B is CH, X is a single bonding arm, A is -CH₂-, and R i's hydrogen atom or a lower alklyl group; compounds group wherein B is CH, X is a single bonding arm, and A s -S-; compounds group wheren B is CH, X is a single bonding arm, and A is -S-; compounds group wheren B is CH, X is a single bonding arm, and A is -S-; and R i's hydrogen atom or a lower alklyl group; and the like may be oxemplified.

[0045] Furthermore, in each of the above-mentioned compound groups, as a more preferred compound group, a group of compounds wherein B is CH, and the compound has the following partial structure:

5 may be exemplified.

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[0046] Also, as specific examples of preferred compounds, the following compounds may be exemplified.

- (S)-2-cyano-1-[t-4-(4-acetyl-1-piperazinyl)-1-methylr-1-cyclohexylamino]acetylpyrrolidine:
- (S)-2-cyano-1-[trans-4-(1,3-dioxo-2-Isoindolinyl)-cyclohexylamino]acetylpyrrolldine;
- (S)-2-cyano-1-(trans-4-morpholinocyclohexylamino)-acetylpyrrolidine; and
- (S)-2-cyano-1-[trans-4-(thiazolo[5,4-b]pyrldin-2-yl)-cyclohexylamino]acetylpyrrolldine, etc.

[0047] The objective compound [i] or a pharmaceutically acceptable salt thereof of the present invention has superior inhibitory action on the enzyme activity of DPPIV. They have superior inhibitory action especially on human DPPIV in addition, they also exhibit high selectivity with respect to DPPIV (namely, type IV dipeptidy) epitidase) in various serine proteases (e.g., plasmin, thrombin, prolylenccoppitidase, trypsin and dipeptidy) epitidase II).

[0048] Also, the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention improves insulin secretion response to oral glucose loading by means of its DPPIV Inhibitory action.

[0049] Thus, the objective compound [i] or a pharmaceutically acceptable salt thereof of the present invention is useful as prophylactic or therapeutic agents for diseases relating to DPPIV (diseases mediated by DPPIV), that is, diseases which is expected to be alleviated by highting DPPIV enzyme activity.

[0050] Examples of such diseases include diseases (e.g., type 1 disabetes and type 2 dishetes), hyperglycemia (such as postprandial hyperglycemia), hyperinsulinemia, disbetes complications (such as renal disorder and neurological disorder), obestly, evereating, lipid metabolism disorder (such as hyperfipemia including hypertrilyceridemia and others), suidimmuno diseases (such as arthritis and rhoumatoid arthritis), ostooporosis, acquired immunodoficiency syndrome (AIDS) and reloction of transplanted organs and dissuer.

[0051] The objective compound [i] or a pharmaceutically acceptable sall thereof of the present invention is particularly useful as a prophylactic or therapeutic agent of diabetes (and particularly type 2 diabetes).

[0052] Further, the compound of the present invention has low toxicity, and thus, has a high level of safety when used as a pharmaceutical compound. Furthermore, it also demonstrates superior pharmacokinatic characteristics [including bloavailability, in vitro metabolic stability (stability in human liver homogenates), P450 inhibitory action and protein binding capabilities, etc.].

[0053] The DPPIV imbitory action of the compound of the present invention as well as its pharmaceulical efficacy (including anti-hyporgycomia effect and the effect of improving insulin secretion response to glucose loading) based on that action can be confirmed by known methods or methods equivalent to those methods (WO 96/1998). WO 00/34241; Holst, et al., Diabetes, Vol. 47, pp. 1683-1670, 1998; Augustyns, et al., Current Medicinal Chemistry, Vol. 6, pp. 311-327, 1999; Meester, et al., Immunol. Today, Vol. 15, pp. 180-184, 1994).

[0064] The objective compound [1] of the present invention can be used for a pharmaceutical use either in a fracform or in a form of a pharmaceutically acceptable salt. Examples of the pharmaceutically acceptable salt of the compound [1] include an inorganic acid salt such as hydrochioride, saltae, phasphato or hydrobromide, and an organic acid salt such as acetale, furnarate, oxiaite, citrate, methanesutlonate, benzenesutlonate, losylate or malcate, etc. in addition, in case that a compound has a substituent(s) such as carboxyl group, a salt with a base for example, an alkall metal salt such as a sodium salt, a potassium salt, etc., or an alkaline earth metal salt such as a calcium salt and the like) may be mentioned.

[0055] The objective compound [I] or the pharmaceutically acceptable salt thereof of the present invention include its internal salts, adducts, solvates and hydrates.

[0058] The objective compound [] or pharmacoulically acceptable salts thereof of the present invention can be administered or vally or parenterally and used ac commonly used pharmaceutical preparations, such as tablets, granules, cassules, powders, injection solution and inhalants. The compound of the present invention, for example, can be used with pharmaceutically acceptable general excipients such as binder, disintegrator, extenders, fillers and lubricants, or diluents, and orepared according to the usual method.

[0057] The administration dose of the objective compound (I) or pharmaceutically acceptable salts thereof of the present invention may vary depending on the administration method, age, weight and condition of a patient, and it is generally about 0.01 to 200 mg/kg, preferably about 0.1 to 30 mg/kg per day.

[0058] The objective compound [i] of the present invention can be prepared according to the following (Process A) to (Process D), but it is not limited to these processes.

(Process A)

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[0059] The objective compound [i] of the present invention can be prepared by reacting a compound represented by the formula [ii]:

wherein Z^1 represents a reactive residue and A has the same meaning as defined above, with a compound represented by the formula [III]:

$$R^2-X-B$$
 NH_2 [III]

wherein R1, R2, B and X have the same meanings as defined above, or salts thereof, and optionally, by making the products into a pharmaceutically acceptable salt.

[0060] As examples of the salt of the compound [III], a salt with an inorganic acid such as hydrochloride and sulfate, or a salt with an inorganic base such as an alkali metal salt and an alkaline earth metal salt can be used

[0061] As the reactive residue of Z1, commonly used reactive residues such as a halogon atom, a lower alkylsulfonyloxy group and an anysulfonyloxy group can be used, among which the helogen atom is particularly preferred. [0062] The reaction of the compound fill with the compound fill for the salt thereof can be carried out in a suitable

[0062] The reaction of the compound [II] with the compound [III] or the salt thereof can be carried out in a suitable solvent or without solvent in the presence or absence of an acid acceptor.

[0063] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, accommittie, methanol, ethanol, scorped alcohol, posten, dimethylformamiel, dimethyls_loxid, totathydrofuran, ether, dioxare, ethyl accitate, and the suitable accitate that the solution of the solution

[0064] This reaction suitably proceeds at 0 to 120°C, particularly at room temperature to 80°C.
[0065] As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali
metal carbonate such as sodium carbonate and potlessium carbonate, alkali metal'alkoxide such as sodium methoxide,
alkali metal' such as sodium, and alkali metal hydroxide such as sodium hydroxide and potassium hydroxide, etc.) or

an organic base (for example, triethylamine, diisopropylethylamine, N-methylmorpholine, pyricine, dimethylaniline, dimethylamine, vican bo suitably used.

(Process B)

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[0066] In addition, among the objective compound [i] of the present invention, the compound wherein R² represents a monocyclic or blcyclic introgen-containing heterocyclic group which may be substituted, and X represents -COO-represented by the formula [I-a]:

wherein R²¹ represents a monocyclic of bicyclic nitrogen containing hetorocyclic group which may be substituted, and 81, A and B have the same meanings as defined above, can be precared by reacting a compound represented by the formula IIVI:

wherein R represents a protective group for the amino group, and R¹, A and B have the same meanings as defined above, or a salt the red with a phospene or an equivalent thereof, and subsequently, further reacting with a compound represented by the formula [VI]:

wherein R21 has the same meaning as defined above, to obtain a compound represented by the formula [VI]:

wherein R; R1, R21, A and B have the same meanings as defined above,

or a salt thereof, and further removing the protective group (R) for the amino group from the product.

[0087] Followed by needing the compound [IV] with a phosgene or an equivalent thereof, the reaction with the compound [V] can be carried out in a suitable solvent or without solvent in the presence of a phosgene or an equivalent thereof and an acid acceptor.

[0068] As "the phosgene or the equivalent thereof", triphosgene, diphosgene, carbonyldilmidazol, 4-nitrophenyl-chloroformate, etc. can be suitably used.

[0069] As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali

metal carbonate such as sodium carbonate and potessium carbonate, alkali metal amide such as sodium amide and lithium amide, alkali metal alkoxide such as sodium methoxide, alkali metal such as sodium, and alkali metal hydroxide such as sodium hydroxide and potassium hydroxide, ofte, of ran, organic base (for example, triethylamine, clisopropylalhylamine, N-methylmorpholine, pyridine, dimethylamiline, dimethylamine, bct.) can be suitably used.

[0070] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and for example, methylene childred, cichlorostems, then, totarhydroutina, eithyl excette, toluene or a mixed solvent thereof can be suitably used. The present reaction suitably proceeds at -78°C to 110°C, especially at 0°C to room temperature.

[0071] The following removal of the protective group (R) for an amino group of the compound [VI] can be carried out of according to the conventional method, and it can be carried out, for example, in a suitable solvent or without solvent by an acid treatment, base treatment or calalytic reduction.

[0072] As the acid, an inorganic acid such as hydrochloric acid, sulfuric acid, etc., and an organic acid such as acetic acid, trifluoroacetic acid, methanesulfonic acid, o-toluenesulfonic acid, etc. can be suitably used

(0073) As the base, an inorganic base (for example, alkall metal hydride such as sodium hydride, etc., akkall metal extronale such as sodium extronale, bitship carbonale such as sodium extronales vach as codium extronales, bitship and etc., alkall metal amide such as sodium, and, alkall metal such as sodium, act., and alkall metal hydroxide such as sodium floroxide, prissation hydroxide, soil or an organic base (for example, triethylamine, inclination propholine, N-methylmorpholine, pyridine, piperdine, dimethylamiline, dimethylamine, morpholine, N-methylmorpholine, pyridine, piperdine, dimethylamiline, dimethylamine, pyridine, piperdine, dimethylamiline, dimethylamine, morpholine, bet.) so the substitution was discovered as the substitution of the subs

[0074] The catalytic reduction can be carried out by suitably using palladium-carbon, palladium hydroxide-carbon, platinum exide or Raney nickel under hydrogen atmosphere.

[0075] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, melhanol, ethanol, isopropyl alcohol, propyl alcohol, dokane, methylene chloride, chloroform, dichlorothane, ether, fetrallydrofuran, ethyl acetate, follene or a mixed solvent thereof can be suitably used.

[0076] This reaction suitably proceeds at -78°C to 80°C, particularly at 0°C to room temperature.

(Process C)

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[0077] In the objective compound [i] of the present invention, the compound wherein B is N, X is -CO-, -Aik-CO- or -SO₂-, represented by the formula [i-b]:

$$R^2-X^1-N$$
 $NH-CH_2-CO-N$
 CN
 $II-b$

wherein X1 represents -CO-, -Alk-CO- or -SO2-, and R1,

R2 and A have the same meanings as defined above, can be prepared by reacting a compound represented by the formula [VIII]:

wherein n is 0, 1, 2 or 3, P represents a resin residue, and R1 and A have the same meanings as defined above, with

a compound represented by the formula [VIII] :

$$\mathbb{R}^2 \cdot V^1$$
 [Viii]

wherein V^1 represents -COOH, -Alk-COOH or a chlorosulfonyl group, and R^2 has the same meaning as defined above, or a salt thereof, and subsequently removing a linker and the resin residue portion represented by the formula f[XI:

$$(OCH_3)_n$$
 [IX]

wherein P and n have the same meanings as defined above, from the reaction product.

[0078] Or else, in the compound (I-b), a compound wherein X^1 is -CO- and R^2 is a carboxy lower alkylene group can be prepared by using a compound represented by the formula [X]:

wherein Aik1 represents a lower alkylene group, in place of the compound [Viii] or a self thereof to carry out the reaction with the compound [VII], and a ubsequently removing the linker and the resin residue portion represented by the formula [IX] from the reaction product.

(Process D)

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fO

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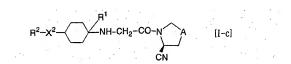
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[0079] Also, in the compound [i], a compound wherein B is CH and X is -CON(R³)-, -Aik-CON(R³)-, or -SO₂N(R³)-, represented by the formula [I-c]:



wherein X^2 represents -CON(R³)-, -Alk-CON(R³)- or -SO₂N(R³)-, and R¹, R², R³ and A have the same meanings as defined above, can be prepared by reacting a compound represented by the formula [XI]:

$$HN$$
 N
 CH_2
 CN
 CN
 OCH_3
 OCH_2
 P

wherein R1, R3, A, P and n have the same meanings as defined above, with a compound represented by the formula [XII]:

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$$R^2-V^2$$
 [XIII]

wherein V² represents -COOH, -Alk-COOH or chlorosulfonyl group and R² has the same meaning as defined above, or a sait thereof, and subsequently removing the linker and the resin residue portion represented by the formula [X] from the reaction product.

[0080] Alternatively, in the compound [I-c], a compound wherein X² is -CON(R³)- and R² is a carboxy lower alkyl. group can be prepared by using a compound [X] in place of the compound [XII] or a sall thereof, reacting the same with the compound [XI], and subsequently removing the linker and the resin residue portion represented by the formula [XI] from the reaction product.

[0081] Also, in the compound [i], a compound wherein B is CH and X is -CON(R³)CH₂- or -Alk-CON(R³)CH₂-, represented by the formula [i-d]:

$$R^2-X^3$$
 NH-CH₂-CO-N A [I-d]

wherein X^3 represents -CON(R^3)CH $_2$ -or -Alk-CON(R^3)CH $_2$ -, and R^1 , R^2 , R^3 and A have the same meanings as defined above, can be prepared by reacting a compound represented by the formula [XIII]:

wherein R¹, R³, A. P and n have the same meanings as defined above, with a compound represented by the formula [XII] or a saft thereof, and subsequently removing the linker and the resin residue portion represented by the formula [XII] from the reaction product.

[0082] Alternatively, a compound [I-d] wherein X^2 is $-CON(R^9)CH_{Z^2}$ and R^2 is a carboxy lower alkyl group can be propared by using a compound [XI] in place of the compound [XIII] or a salt thereof, reacting the same with the compound [XIII], and subsequently removing the linker and the resin residue portion represented by the formula [IX] from the reaction product.

(Reactions in Process C and Process D)

[0083] The reactions in Process C (the reaction between the compound [VI] and the compound [VIII] or a salt thereof (or the compound [XII), and the reactions in Process D (the reaction between the compound [XII] or [XIII] and the compound [XIII] or a salt thereof (or the compound [XIII) can be carried out, optionally in the presence of a condensing agent and/or an acid acceptor, in a suitable solvent or without solvent. Further, the linker and the resin recidue portion are removed according to the conventional method, and if necessary, purification is carried out by, for example, extraction, distribution, reprecipitation, crystallization, recrystallization, various kinds of chromatographies, high performance chromatography, etc.

[0084] As the linker, a group in which a resin residue (P) portion is removed from the group represented by the formula [IX] can be exemplified.

[0085] As the resin residue represented by P, a resin that is used in a conventional solid phase synthesis can be used, and there may be mentioned, for example, a Merrifield resin (4-chloromothyl polystyrene resin, etc.), a Wang resin (4 bercytocytocytocytocyta) alcohol resin, etc.), a typicatymothyl polystyrene resin, etc.), etc. As the kinds of resin, any resin may be used as long as it does not adversely affect to the reaction, and it is suitably selected depending on the kind of the objective compound. Generally, those with a particle diameter of 70 to 200 µm are preferably used, and a leading cascalty is orderelably 0.1 to 2 mmol/c.

[0086] As the condensing agent, O-benzotriazoi-1-yi-N,N,N',N'-tetramethyluroniumhexafluorophoschate, DCC (dicyclichexylec/bodilind), EDC (1-ethyl-3-(3-dimethyl-aminopropyl)carbodilindle), olthoroformaties (for example, ethyl hidroformate and isobuty olthoroformate) and carbonyldimitactoe, acc. can be suitably used. Also, for promoting the reaction, an additive such as a base (sodium carbonate, sodium hydrogencarbonate, triethylamine, pyridine, 4- dimethylaminopyridine, dileopropylethylamine, 1,8-diszabloyalo[5.4.0]undeo-7-ene, etc.), 1-hydroxybenzotriazole, 1-hydroxyeucchimide, ct. can be added to the above condensine agent.

[0087] As the exid acceptor, alkali metal hydroxide such as sodium hydroxide and potassium hydroxide, alkali metal by hydrogenerabronate such as sodium hydrogenerabronate such as sodium hydrogenerabronate such as sodium exidencerabronate such as sodium orarbonate such as sodium carbonate and potassium carbonate, an organic base (triethylamine, pyridine, etc.), etc. can be suitably used.

[0088] The following removal of the linker and the resin residue portion can be suitably carried out in a suitable solvent or without solvent by treating the product with trifluoraceatic acid, influoromethanesulfonic acid, hydrogen fluoride, hydrogen bromide, hydrogen chloride, etc. and a mixture thereof.

[0089] As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, methylene chiloride, N-methyl morpholine, dimethylformamide, tetrahydrofuran, dimethylacetamide or a mixed solvent thereof can be suitably used.

[0990] The reaction in Process C suitably proceeds at 0 to 120°C, particularly at 20 to 50°C. And the reaction in Process D suitably proceeds at 0 to 50°C, particularly at 0 to 30°C.

[0091] As the solvent to be used in the following reaction for removing the linker and the resin residue portion, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, methylene chloride, acetic acid, trifluoroacetic acid or a mixed solvent thereof can be suitably used. The reaction suitably proceeds at 0 to 50°C, particularly at 0 to 30°C.

(Starting material for Process A)

[0092] The starting material [III] of the present invention can be prepared, for example, according to the process described in International Patent Publications Nos. WO98/19998, WO00/34241 and Reference Examples mentioned below (Reference Example 1 or 2), etc.

[0093] For example, the compound [II] can be obtained by reacting a compound represented by the formula [20]:

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wherein A has the same meaning as defined above, with a compound represented by the formula [21]:

wherein Z² and Z³ represent a reactive residue which may be the same or different, in the presence of an acid acceptor (for example, trethylamine, etc.) to obtain a compound represented by the formula (22):

$$Z^2$$
-CH₂-CO-N A [22]

wherein Z2 and A have the same meanings as defined above,

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and treating the product with a dehydrating agent (for example, phosphorous oxychloride, trifluoroacetic anhydride, etc.) according to the conventional method.

[0094] As the reactive residue of Z² or Z³, the same reactive residue commonly used as mentioned above Z¹ can be sultably used.

[0095] The starting material [III] can be prepared, for example, by the same process as described in Reference Examples mentioned below (Reference Examples 7 to 10).

[0096] For example, the compound [III] wherein X is -O-CH₂-or-NHCH₂- can be prepared by reacting a compound represented by the formula [23]:

$$V^3$$
— CH_2 — B
 NH_2
[23]

wherein V³ represents a hydroxy group or an amino group, and R¹ and B have the same meanings as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [24]:

wherein Z⁴ represents a reactive residue and the other symbol has the same meaning as defined above, in the presence or absence of an acid acceptor (for example, an organic base such as triethylamine, disopropylethylamine, etc., and an inorganic base such as sodium hydride, potassium carbonate, etc.), and, if necessary, removing the protective group for the amiling group according to the conventional method.

[0097] As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0098] As the reactive residue of Z⁴, the same reactive residue commonly used as mentioned above Z¹ can be suitably used.

[0099] Also, the compound [III] wherein X is -Alk-O- or -S- can be prepared by reacting a compound represented by the formula [25]:

$$V^4-B$$
 R^1
 NH_2 [25]

wherein V⁴ represents a hydroxy group or a mercapto group and R¹ and B have the same meanings as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [26a] or the formula [26b]:

or

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wherein Z51 and Z52 represent a reactive residue and

R⁶ and Alk have the same meanings as defined above, in the presence or absence of an acid acceptor (for oxample, an organic base such as triethylamine, discopropylethylamine, etc., and an inorganic base such as sodium hydride, potassium carbonate, etc.), and, if necessary removing the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R of an be suitably used.

[0100] As the reactive residue of Z⁵¹ and Z⁵², the same reactive residue commonly used as mentioned above Z¹ can be suitably used.

[0101] Also, the compound [III] wherein X is -COCH₂N(R³)- or -SO₂N(R³)- can be obtained by reacting a compound represented by the formula [27]:

$$V^5-B$$
 R^1
 NH_2 [27]

wherein V⁵ represents -N(R³)H, and R¹, R³ and B have the same meanings as defined above, an amino groupprotected material thereof or a salt thereof with a compound represented by the formula [28a] or the formula [28b]:

$$R^2$$
-COCH₂- Z^{81} [28a]

or

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$$R^2$$
-SO₂-Z⁶² [28b]

wherein Z⁶¹ and Z⁶² represent a reactive residue and R² has the same meaning as defined above, in the presence or absence of an acid acceptor (for example, an organic base such as utellylamine, disc), and an inorganic base such as sodium hydride, potassium carbonate, etc.), and, if necessary, removing the protective group for the amino group according to the conventional method. As the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as a mentioned above R can be suitably used.

[0102] As the reactive residue of Z⁶¹ and Z⁶², the same reactive residue commonly used as mentioned above Z¹ can be sultably used.

[0103] Also, the compound [III] wherein X is -CON(R³)-, -Alk-CON(R³)- or -SO₂N(R³)- can be prepared by reacting the compound represented by the formula [27], an amino group-protected material thereof or a sait thereof, with a

compound represented by the formula [29] :

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$$R^2 - V^6$$
 [29] [29]

wherein VF represents COOH, Alk-COOH or SO₂H and RP has the same meaning as defined above, or a sait thereof in the presence of a condensing agent (1-ethyl-3-d-3-dimethylaminopropyl)carhoodimide, etc.), and, if necessary, removing the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0104] Also, the compound [III] wherein X is -CON(RP)CH₂- or -Alk-CON(RP)CH₂- can be prepared by reacting a compound represented by the formula [30].

$$V^7$$
_CH₂—B NH_2 [30]

wherein V⁷ represents -N(R⁹)H, and R¹, R³ and B have the same meanings as defined above, an amino groupprotected material thereof or a salt thereof, with a compound represented by the formula [31]:

wherein V⁸ represents -COOH or -Alk-COOH and R² has the same meaning as defined above, or a salt thereof in the presence of a condensing agent (1-ethyl-3-(3-dimethylaminopropyl)carbodilmide, etc.), and, if necessary, removing the projective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mertifioned above R can be suitably used.

[0165] Also, the compound [iii] wherein B is H, X is ~CO- or ~Alk-CO- and R² is (1) a monocyclic or bicyclic nitrogencontaining halencopylic group which may be substituted or (2) an amino group substituted by 1 or 2 substituted as elected from a substituted or unsubstituted lower alkyl group, represented by the formula.

can be prepared by reacting a compound represented by the formula [32]:

$$V^9$$
 NH_2 [32]

wherein V⁹ represents -COOH and R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof, with a compound represented by the formula (33a):

wherein R²² represents (1) a monocyclic or bloyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substituents selected from a substituted or unsubstituted lower alkyl group, represented by the formula:

$$\bigcirc$$
N $-$

and Alk has the same meaning as defined above, or a salt thereof, in the presence of a concensing againt [1-ethyl-5/4-5/ethirdhylminorpopy)(settodimide, etc.), and II necessary, removing the protective group for the aming oppulaceording to the conventional method. As the protective group for the aming orgup, any of the same protective groups commently used as mentioned above Fican be suitably used.

[016] Also, the compound [iii] wherein B is N, X is -CO- or -Alk-CO- and R² is (1) a monocyclic or bicyclic nitrogencontaining heterocyclic group which may be a bestituted or (2) an amino group substituted by 1 or 2 substituent a selected from a substituted or ursubstituted lower akyl group, represented by the formula.

can be prepared by reacting a compound represented by the formula [330].

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wherein R1 has the same meaning as defined above, an amino group-protected material thereof or a sait thereof, with the compound represented by the formula [331] or [332]:

wherein R²² represents (1) a monocyclic or bicyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substituents selected from a substituted or unsubstituted lower ally/ group, represented by the formula:

and Z^T represents a reactive residue, or a salt thereof, in the presence or absence of an acid acceptor (for example, an organic base such as a solium hydride, potassium carbonate, etc.), and, if necessary, removing the profective group for the amino group according to the conventional method. As the protective group for the arrino group, any of the same protective groups commonly used as mentioned above T can be suitably used. As the reactive residue of Z^T , the same reactive residue commonly used as mentioned above T can be suitably used.

[0107] Also, the compound [III] wherein B is CH, X is a single bonding arm and R² is (1) a monocyclic or bicyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substituents selected from a substituted or unsubstituted lower alkyl group, represented by the formula:

can be prepared by reacting the compound represented by the formula [34] :

$$O = \begin{pmatrix} R^1 \\ NH_2 \end{pmatrix} [34]$$

wherein R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof, with a compound represented by the formula [33b]:

wherein R²² has the same meaning as defined above, in the prosence of a reducing agent (sodium triacetoxy-borohydride etc.), and, if necessary, removing the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0108] Also, the compound [III] wherein B is CH, X is a single bonding arm and R² is a group represented by the formula:

can be prepared by reacting a compound represented by the formula [35]:

$$H_2N$$
 $\begin{array}{c} & R^1 \\ & NH_2 \end{array}$
 $\begin{bmatrix} 35 \end{bmatrix}$

wherein R[†] has the same meaning as defined above, an amino group-protected material thereof or a sait thereof, with a compound represented by the formula [36]:

wherein Ar represents an arylene (phenylene, etc.) which may have a substituent(e), in the presence or absence of an acid acceptor (for exampic, an organic base such as tricintylamine, discopropylethylamine, etc., and an inorganic base such as sodium hydrific, potassium carbonate, etc.), and, if necessary, removing the protective group for the amino group according to the conventionel method. As the protective group for the amino group, any of the same protective groups commently used as mentioned above R can be suitably used.

[0109] Also, the compound [III] wherein B is CH, X is a single bonding arm and R² is a nitrogen-containing heterocyclic group represented by the formula:

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can be prepared by reacting the compound represented by the above-montloned formula [35], an amino group-protected material thereof or a salt thereof, with a compound represented by the formula [37]:

$$Z^{81}$$
 [37]

wherein Z⁹¹ and Z⁵² both represent a reactive residue, or a sait thereof, in the presence or absence of an acid acceptor (for exemple, an organic base such'as trieflylamine, discopropylethylamine, due, and an inorganic base such as sodium hydride, polassium carbonate, etc.), and, if necessary, removing the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0110] As the reactive residue of Z⁸¹ and Z⁸², the same reactive residue commonly used as mentioned above Z¹ can be suitably used.

[0111] Also, the compound [III] wherein B.is N and X is a single bonding arm can be prepared by reacting a compound represented by the formula [38]:

wherein R¹ has the same meaning as defined above, an amino group-protected material thereof or a salt thereof, with the compound represented by the above-mentioned formula [24]:

wherein R² and Z⁴ have the same meanings as defined above, in the presence or absence of an acid acceptor (for example, an organic base such as triethylamine, disoppropriethylamine, due, and an inorganic base such as addium hydride, potassium carbonate, etc.), and, if necessary, removing the protective group for the amine group according to the conventional method. As the protective group for the amine group, any of the same commonly used protective groups as monthlored above R can be suitable used.

[0112] Also, the compound [III] wherein X is -COO- can be prepared by reacting an amino group-protected material or a salt of a compound represented by the formula [39]:

$$HO-B \longrightarrow NH_2$$
 [39]

wherein R1 and B have the same meanings as defined above, with a compound represented by the formula [40]:

wherein R² has the same meaning as defined above, in the presence of an acid acceptor (dimethylaminopyridine, etc.), and, if necessary, removing the protective group for the amino group according to the conventional method. As the protective group for the amino group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0113] The starting materials [20] to (40] can be prepared according to the known methods or in the same manner as mentioned in Reference Examples below. In the starting material [III] wherein B is Cit, ustrans isomers are present, taking a cyclohexane ring as a standard plane. In this case, it is possible to obtain a desired form of isomer of the starting acyclohexane compound, corresponding to each of desired products.

[0114] Alternatively, a mixture of cis/trans isomers is obtained as a starting material [III], and then, a desired isomer can be separated by means of chromatography, etc.

(Starting material of Process B)

[0115]

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wherein R, R1, Z1, A and B have the same meanings as defined above.

[0116] A compound represented by the formula [IV] or a salt thereof can be prepared by reacting the compound represented by the above formula [II] with a compound represented by the formula [41] or a salt thereof to obtain a compound represented by the formula [42] or a salt thereof, and further reacting the same with a compound represented by the formula [43] or the formula [44].

[0117] Reaction between the compound [1] and the compound [41] or a salt thereof can be carried out in the presence or absence of an acid acceptor, in a suitable solvent or without solvent, as the solvent, any solvents may be suitable as long as it is not adversely affected to the 'reaction, and, for example, accloritile, methand, ethand, isopropyl alcohol, propyl alcohol, acetone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, ether, dloxane, ethyl accitate, tollene, methylene chloride, dichlorochiane, chloroform or a mixed solvent thereof can be suitably used. This reaction sulfably proceeds at 0 to 120°C, carbicularly at room temporature to 80°C. [0118] As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali motal carbonate such as sodium carbonate, and alkali motal alkoxide such as sodium methoxide, alkali motal such as sodium, and alkali motal hydroxide such as sodium hydroxide and potassium hydroxide, etc.) or an organic base (for example, triethylamine, diisopropylethylamine, N-methylmorphotine, pyridine, dimethylamine) and providine, etc.) can be suitably used.

[0119] Reaction between the compound [42] or a salt thereof and the compound [43] or [44] can be carried out in the presence of an acid acceptor, in a suitable solvent or without solvent.

[0120] As the solvent, any solvents may be suitable as long as it is not adversely affected to the reaction, and, for example, accountriel, methanol, eltanol, isopropyl alcohol, propyl alcohol, accidente, letrahydrofuran, ether, dioxane, ethyl acetaet, toluene, methylene chloride, dichloroethano, othoroform, water or a mixed solvent thereof can be suitably used. This reaction suitably proceeds at 0 to 120°C, particularly et room temperature to 80°C.

[0121] As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali metal carbonate such as sodium reathonate and potassium carbonate, alkali metal sociale such as sodium methoxide, alkali metal sociale sodium sodium sodium sodium sodium sodium hydroxide, such as sodium hydroxide, such as sodium hydroxide, such carbonate in sodium so

(Starting materials of Process C and Process D)

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[0122] The compound [VII], the compound [IX] or the compound [XIII] can be each obtained by reacting a compound represented by the formula [50], [51] or [52]:

wherein V¹⁰, V¹¹ and V¹² represent protective groups for the amino group, and R¹ and R³ have the same meanings as defined above, with a compound represented by the formula [53]:

wherein P and n have the same meanings as defined above, according to a conventronal method, in the presence of a reducing agent (for example, sodium triacetoxyborohydride, etc.), subsequently reacting the product in the presence of the compound [II] and an acid acceptor (dileopropylethylamine, etc.), and then, removing the protective group for the amine group according to the conventional method. As the protective group for the amine group, any of the same protective groups commonly used as mentioned above R can be suitably used.

[0123] The compound [I] of the present invention or its starting material prepared according to the above is isolated in a free form or as a salt thereof, and purified. Salts can be propared by subjecting to the salt-forming treatment conventionally used.

[0124] Isolation and purification can be carried out by applying the usual chemical operations such as extraction, concentration, crystalization, illitration, recrystalization, various kinds of chromatographics and the like (0125). For the compound of the present invention and a starting material thereof, optical isomers, such as recentic.

[0125] For the compound of the present invention and a starting material thereof, optical isomers, such as racemic modifications, optically active substances, diastereomers, etc. can be present alone or as mixtures the

[0126] A stereochemically pure isomor can be derived by using a stereochemically pure starting material or by separating an optical isomer according to the general separation process for racomic resolution. Also, disastereometic mixtures can be separated according to the conventional method, for example, fractional crystallization or by chromatography.

EXAMPLES

[0127] The present invention will be described in detail by referring to the following Examples but these Examples do not intend to limit the present invention.

Example 1-1

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[0138] An acetohitine-methanol solution containing 100 mg of (5)-1-bromoacestyl-2-cyanopyrrolidine (Reference Example 1 mentioned below) and 247 mg of 4-amino-1-(2-pyrindinyl)-piperidine (Reference Example 7-1 mentioned below) was clirred at room temperature for 15 hours. Water was added to the reaction mixture and the mixture was extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed uncer reduced pressure. The residue was purified by did column chromatography (solvent: 0 to 10% methanol-chloroform), and dissolved in 0.5 ml of ethyl acetate-0.5 ml of chloroform. Added thereto were 1.0 ml of 2N hydrochloric acid-other, collowed by 2 ml of other. The resulting precipitates were collected by filtration and washed with either to obtain (S)-2-cyano-1-(1-(2-pyrtindinyl)piperidin-4-ylamino)-acetylpyrrolidine/dihydrochlorida (Example 1-1 in Table 1), Examples 1-2 to 1-19.1 1-32 to 1-10.3 to 1-10.3 to 1-10.3

[0129] The compounds of Table 1 shown below (Examples 1-2 to 1-30, 1-92 to 1-109) were obtained in the same manner as in the above-mentioned Example 1-1 by using (s)-1-bromoacotyl-2-cyanopyrrolidine and cornosponding starting materials. (Provided that the compound of Example 1-38 was obtained as a by product of Example 1-33, (The corresponding starting materials were obtained in the same manner as described in Reference Examples mentioned below, by known methods or by a method in combination of these methods.)

Example 1-91

(0130) 570 mg of (5)1-to-romoecely1-2-cyanopyrrolidine was added to 6 ml of an acetontrile solution containing 300 mg of trans-1-d-cyclohexanedlamine and 457_u fol NN-diloc-propylethylamine, and the mixture was attirred at room temperature for 3 hours. The reaction mixture was diffued with brino and extracted with chloroform. After the extract was dired over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by allica gel column chromatography (solvent: chloroform-manhanol (100-0 to 95.6)) to obtain an oily product. The pulp reduct was cissolved in 0.5 ml of brioroform, and added thereto were 0.5 ml of 11 N hydrochloric acid-other, followed by 4 ml of ether. The resulting precipitates were washed with ether to obtain 307 mg of (5)-cyanon-1-(trans-4-(5) -(2-cyano-1-pyrolidInyi)carbonyimethylamino|cyclohexylamino|acetyloyrrolidine dihydrochloride (Example 1-91 in Table 1).

35 Examples 2-1 to 2-9

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- (1) A mixture comprising 600 mg of 4-tent-butoxycarbonyl-amino-4-methylcyclohaxanone (the compound of Reference Example 6-1 (3)). 783 mg of sodium trisectoxylorotydride, 252 mg of morpholine, 156 mg of accidic acid and 6 mi of dichiorosthane was stirred at room temperature for 16 hours. The mixture was disuted with an aqueous saturated sodium hydrogencarbonate solution and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica goji column chromatography (solvent: chloroform-methanol (20-1) to chloroform-methanol (21-1) + 1% aqueous ammonia) to obtain 600 mg of a mixture of N-tert-butoxycarbonyl-1-methyl-4-d-morpholino-1-1-dyclohaxylamine (Reference Example 8-64; a compound before deprotection). 220 mg of this compound was aftered in a mixted solution of 2 mi of 4N hydrochloric acid-dioxane and 2 mild of sthanol at room temperature for 15 hours to deprotect the N-tert-butoxycarbonyl group, and then, the reaction mixture was concentrated to obtain a residue.
 - (2) To the compound obtained in the above (1) were added 320 mg of (S)-1-bromoscelyl-2-cyanopyrrolidine, 0.6 ml of triethylarnine, 3.5 ml of acetonitrile and 1 ml of methanol, and the mixture was siliered at room temperature for 15 hours. The mixture was diffued with an aqueous saturated sodium hydrogener/bronate solution and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silicia gel column chromatography (solvent: chloroform-hoxano (1:1) to chloroform) to obtain 2 kinds of oil by orducts.

[0132] The compound with lower polarity was treated with hydrochloric acid to obtain 33 mg of (S):2-cyanc-1-[1-me-thyl-c-4-morpholino-r-1-cyclohexylamino]acetylpyrrolidine'dihydrochloride (Example 2-1 in Table 2). Also, the com-

pound with higher polarity was treated with hydrochloric acid to obtain 82 mg of (S)-2-cyano-1-[1-methyl-t-4-morpholinor-1-cyclohexylamino]acotylpyrrolidine dihydrochloride (Example 2-2 in Table 2).

[0133] The compounds of Examples 2-3 to 2-9 in Table 2 were obtained in the same manner as mentioned above.

5 Example 3

[0134]

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- (1) To 60 ml of acetontrile-methanol (3/1) mixod solution containing 4.78 g of trans-4-aminocyclohoxanol was added 3.00 g of (5)-1-bromoscotyl-2-cyanopyrrolidine under loe-cooling, and the mixture was stirred at room temperature for 14 hours. To the reaction mixture were added 1.93 ml of triethylamine, followed by 16 ml of an acetoritrile solution containing di-tert-butydicarbonate at room temperature, and the mixture was stirred for 3 hours as such. After the solvent was removed under raduced pressure, water was added to the residue, and then neutralized with an aqueous sodium hydrogencarbonate solution. The mixture was then extracted with chloroform, dried and concentrated. The obligationed residue was purified by sitics get column chromatography to obtain 4.72 g of (5)-1-(4-ret-butoxy-carbonyl-trans-4-4-floxy-ret-volcoty-cyano-pyrolidio).
 - (2) 84 mg of triphosgene was added to 2 ml of a methylene chloride solution containing 150 mg of the compound obtained in the above (1) and 12 μ. of pyridine at room temperature, and the mixture was stirred of 1 hour as such. Subsequently, to the mixture was added 1 mL of a methylene chloride solution containing 186 μ. of morpholine, and the mixture was stirred at room temperature for 1 hour and diluted with an equeous citric acid colution. The mixture was extracted with eithyl acetato, dried and concentrated. Subsequently, it was purified by silica gol column chromatography to obtain 174 mg of (S)-1-(N-tent-butoxycarbonyl-trans-4-(morpholinocarbonyloxy)cy-obtoxyl-aminolaetyl-2-cynagovroriddine.
- (3) 157 mg of the compound obtained in the above (2) was dissolved in 1.5 mL of trifluoroscetic acid and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and then, an aqueous sodium hydrogencarbonate solution was added to the residue, making the solution alkaline. The mixture was extracted with othordorm, dried and concentrated. Subsocuently, the resulting residue was purified by column chromatography (solvent) to 55 methenci-foliorical price and an oily product. This was dissolved in 1 mL of ethyl acetate and added thereto were 0.5 mL of 1N hydrochloric acid-ether, followed by 2 mL of ether. The resulting precipitates were washed with ether to obtain 97 mg of (5)2-cyano-1-[trans-4-(morpholinocarbonyloxy) cyolohexylaminojacetylpricellane hydrochloride (Exemple 3 in Table 3).

Example 4-1

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- (1) A mixture comprising 500 mg of the resin compound obtained in Reference Exemple 3 (2) mentioned below and 0.5M methanesulfonic acid in dioxanc-mothylone chloride (1/8) was stirred at room temperature for 18 hours. The resin was collected by filtration and washed with dimethyl formamide, 10% triethylamino-methylone chloride, dimethylformamide-water (1:1), methanol, tetrahydrofuran, methanol and methylone chloride. A mixture comprising the obtained resin, 277 µl of benzyl isocyanate and 4 ml of methylone chloride was stirred at room temperature for 18 hours. The resin was collected by filtration and washed with dimethylformamide, dimethylformamide-water (1:1), methanol, tetrahydrofuran, methanol and methylene chloride, and dried under reduced pressure to obtain a
 - (2) A mixture comprising the resin obtained in the above (1) and 4 mid of tifluoreacello acid was stirred at room temperature for IR amours. The resin was removed by filtration and washed with metrylene chloride, and the filtrate and the washing solution were combined and concentrated. To the resulting residue was acided an aqueous sodium hydrogenizationate solution, thereby making the solution alkeline. Subsequently it was accracted with chloroform, dried and concentrated. The obtained residue was purified by did column chromotography (solvent: 10 a 5% methics) and chloroform) to obtain an oily product. This was dissolved in 0.5 mil of thyl acctate and added thereto were 0.5 mil of 1 N hydrochloric acid-ether, followed by 2 mil of citer. The resulting precipitates were washed with enter to obtain (5)-2-cyano-1-[1-(benzylaminocarbonyl)piperidin-4-ylamino)-acetylpyrrolidine/hydrochloride (Example 4.1 in Table 4.)

55 Examples 4-2 to 4-5

[0136] The compounds of Examples 4-2 and 4-3 in Table 4 were obtained in the same manner as in Example 4-1, using the corresponding starting materials (isocyanate compounds). Also, the compounds of Examples 4-4 and 4-5 in

Table 4 were obtained in the same manner as in Example 4-1, using intramolecular cyclic anhydride of dicarboxylic acid (succinic anhydride and glutaric anhydride) as starting materials in place of the isocyanate compound.

Examples 4-6 to 4-10

[0137] The compound of Examples 4-6 in Table 4 was obtained in the same manner as in Example 4-1, except for using methylchioroformate as a starting material in place of benzyl isocyanate, and carrying out the reaction of the section (1) in the presence of triethylamine. Also, the compounds of Examples 4-7 to 4-10 were obtained in the same manner as mentioned above, using a corresponding starting meterial (chloride).

Example 4-11

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[0138] A mixture comprising 500 mg of the resin compound obtained in the Reference Example 3 (2) and 0.5M methanesuffonic acid in dioxan-frvethylene chloride (1/6) was stirred at room temperature for 18 hours. The resin was collected by fittration and was washed with directhylformamide, 10% triethylamine-methylene chloride, dimethylformamide-water (1:1), methanol, tetrahydroluran, methanol and methylene chloride. A mixture of the obtained resin, 177 mg of 2-quintifinecarioxylic sold, 138 mg of 1-hydroxy-benzotitezol, 387 mg of 0-benzotitizaci 1-y-N,N,N,N-1477am-ethyluronium hexaflurorphosphase, 224 ml of N-methylmorphosine and 4 ml of dimethylformamide was stirred at room temporature for 18 hours. The rosin was collected by filtration and weashed with dimethylformamide, dimethylformamidewater [1:1), methanol, letrahydrofuran, methanol and methylene chloride, and dried under reduced pressure to obtain a resin. This resin was treated with tifluroracetic acid in the same manner as in Example 4-1 (2) to obtain 136 mg of \$(3)-2-yano-1-[1-(2-quinto)|schartphyl-piprintint-4-yalmino|scartphyrorlidinted|thyrochothide (Example 4-1) in Table of \$(3)-2-yano-1-[1-(2-quinto)|scartphyl-piprintint-4-yalmino|scartphyrorlidinted|thyrochothide (Example 4-1) in Table of \$(3)-2-yano-1-[1-(3)-quinto)|scartphyl-piprintinted|thyrochothide (Example 4-1) in Table of \$(3)-2-yano-1-[1-(3)-quinto)|scartphyl-piprintinted|thyrochothide (Example 4-1) in Table

Examples 4-12 to 4-19

[0139] The compounds of Examples 4-12 to 4-19 in Table 4 were obtained in the same manner as in Example 4-11 by using corresponding starting materials (carboxylic acid compounds).

Examples 5-1 to 5-12

[0140] The compounds of Examples 5-1 to 5-12 in Table 5 were obtained in the same manner as in Examples 4-1 to 4-10 by using a resin compound obtained in Reference Example 4 in place of the resin compound of Reference Example 3 (2) Examples 5-13 to 5-36

[0141] The compounds of Examples 5-13 to 5-30 in Table 5 were obtained in the same manner as in Example 4-1, using a resin compound obtained in Reference Example 4 in palse of the reside compound of Reference Example 4-1 in palse of the reside compound of Reference Example 4 in palse 6 were obtained in the same manner by using a resin compound obtained in Reference Example 5 (5).

Examples 5-37 to 5-39

[0142] A mixture comprising 500 mg of the resin compound obtained in the Reference Example 5 (5) and 0.5M methanesulfonio acid in dioxane/methylene chloride, (19) was shaken at room temperature for 30 minutes. The resin was collected by filtration and was washed with methylene chloride, 10% tiethylamine-methylene chloride, dimethylformamide, water (1:1), tetrahydrofuran, methanol, totrahydrofuran, methanol, and dimethylformamide, dimethylformamide water (1:1), tetrahydrofuran, methanol, totrahydrofuran, methanol, and dimethylformamide, water of the bottained reals. 290 mg 0? 2-chloro-5-brompoyrimidien and 211 µ of trabity-mamine was shaken at 55°C for 16 hours. The resin was collected by filtration and washed with dimethylformamide, methylene chloride, 10% trethylamine-methylene chloride, methylone chloride, whose treatment of the chloride collected by filtration and washed with dimethylformamide-water (1:1), tetrahydrofuran, methanol, tetrahydrofuran methylone chloride. Whole amount of the obtained resin was treated with influoroacetic acid to obtain 61 mg of (5)-1 (frans-4-(5-brompyrimidin-2-ylaminomethyloycoloray-aminologany-2-vanopprovidine hydrochlorade (Example 5.3° 1. Trable 5).

[0143] Also, the compounds of Examples 5-38 to 5-39 were obtained in the same manner by using corresponding starting materials.

Example 6-1

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(1) A mixture comprising 519 mg of trans-4-(tert-but/oxy-carbonylaminomethyllcyclohexylamine (Reference Example 5 (3) mentioned below), 446 mg of 2.4,6-trimethoxybenz-aldehyde, 608 mg of sodium triacetoxybornlydride and 11 m. of methylene chioride was stirred at room temperature for 14 hours. The reaction mixture was cilluted with an aqueous saturated sodium hydrogenearoonate solution and extracted with chioroform. The extract was washed with brine, dired ever anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent: 0-20% methanoi-chioroform). A mixture of the obtained compound (989 mg), 641 mg of (5)-1-tomonacepti-2-cyanopyrrolldine, 791 µd of disporpoyleritylamine and 8 ml of dimethylacetamide was attirred at 50°C for 1 hour. The reaction mixture was diluted with water and oxtracted with ethyl acetalate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent: 50-0% haxane-chioroform) to obtain 834 mg of (5)-2-cyano-1-(1-N-2,4,6-trimethoxyphenylmethyl)-trans-4-(tert-butoxycarbonylaminomethylhycyclohexylaminolegotyl-provriolline.

(2) A mixture comprising B18 mg of the compound obtained in the above (1) and 20 mL of 0.5M methanesulfonic acid in dioxane/methylene chloride (1/9) was stirred at room temperature for 2 hours. The reaction mixture was diluted with an aqueous saturated sodium hydrogenearbonate solution and extracted with chlorion. The extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed underreduced pressure to washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed underreduced pressure to washe 44 minor-methyl)cyclohaxylamino] accept/pyrrolidine.

(3) A mixture comprising 155 mg of the compound obtained in the above (2), 104 mg of 2.5-dichleropyrimidine, 146 µL of trienthyldrine, 1 mL of tetrshydrofuren, and 1 mL of dimethylformarride was stirred at 60°C for 14 hours. The reaction mixture was districted with water, and extracted with ethyl acctate. The extract was washed with water and brine, dried over anhydrous socium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent: 0-05% methanol-(35% hexare-chlorofur)) to obtain 104 mg of (5)-2-cyano-1-[N-(2,4)-trimothoxypheny methyl)-trans-4-(6-chloropyrimidin-2-ylaminomethyl)cyclobxytaminogactyl-pyrroidine.

(4) A mixture comprising 90 mg of the compound obtained in the above (3) and 4 mL of trifluoroacetic acid was attirred at nom temperature for 18 hours. After trifluoroacetic acid was removed under reduced pressure, an aqueous asturated sodium hydrogenearbonate solutions was added to the residue, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent 40-0% hexane-chloroform). The obtained compound was dissolved in 0.5 mL of chloroform, and were added thereto 0.5 mL of 11 h hydrochloric acid-ether, followed by 2 mL of ether. The resulting precipitates were washed with ether to obtain 22 mg of (§)-1-ftrans-4-(5-chloropyrimidin-2-yiaminomethyl)cyclohoxylamino]acetyl-2-cyanopyrrolldine dihydrochloride (Example 6-1 in Table e 8).

Examples 8-2 to 6-4

[0144] The compounds of Examples 6-2 to 6-4 in Table 6 were obtained in the same manner as in Example 6-1 (3)

and (4) by using the compound obtained in the above Example 6-1 (2) and corresponding starting materials,

Examples 7-1 to 7-10

[0145] The compounds of Examples 7-1 to 7-10 in Table 7 were obtained in the same manner as mentioned above Example 1 by using (R)-3-chloroacetyl-4-cyanothiazoildine (a compound in Reference Example 2 mentioned below) in place of (S)-1-bromoacetyl-2-cyanopyrrioidine.

Examples 8-1 to 8-8

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[0146] (R)-4-cyano-3-[N-(2.4,6-t/methoxypheny/methy)-trans-4-aminomethylcyclohexylaminojacelylihiazolidine was oblained in the same manner as in Example. 6-1 (1) and (2) by using (R)-3-chloroacetyl-4-cyanothiazolidinein place of (S)-1-bromoacetyl-2-cyanopyrrolidine. By using this compound and corresponding starting materials, the compounds of Examples 8-1 to 8-8 in Table 8 were obtained in the seme manner as in Examples 6-1 (3) and (4). (Provided that in case of Examples 8-1 and 8-8, in the process corresponding to Example 6-1 (3), a catoxylic acid compound was used as a starting material, and the reaction was carried out in the presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylam reopropy)-carolidinice)

Reference Example 1

[0147] According to the process described in the literature (WO98/19998), (S)-1-bromoacelyl-2-cyanopyrrolldine was obtained by reacting L-prolineamide (commercially available product) and bromoacelyl bromide, followed by dehydration. Reference Example 2

[0148] L-thioprolineamide hydrochloride was synthesized according to the process described in the literature (Ashworth et. al., Boorg. Med. Chem. Lett., Vol. 6, pp. 2745-2748, 1986), 2.38 ml of othioracetyl chioride was added to 150 ml of a dichloromethane solution containing 5.00 g of the thus obtained L-thioprolineamide hydrochloride and 6.87 ml of triethylamine under loe-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added 4.8 ml of pylidine and 8.4 ml of trifluoroacetic anhydride, and the mixture was further stimed at room temperature for 1 hour. The reaction mixture was washed with an aqueous 10% HCl solution and water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Subsequently, the residue was crystallized from either to obtain 4.82 or (16%-othoroscolvid-overnthiagoldine as a velowish brown cryste).

(1) A mixture comprising 14.5 g (1.40 mmol/g) of a resin ((4-formyl-3,5-dimethoxyphenyloxy)methyl polystyrene) [synthesized according to a method of Cecile Pegurier et al., (Bioorg. Med. Chem., Vol. 8, pp. 183-171, 2000), 7.85 g of 4-amino-1-tart-buoxycarbonylpiperidine, 10.71 g of sodium trisectoxybornhydride, and 180 m of methylene chloride was stimod at room temperature for 18 hous. The resin was collected by filtration, and washed with methylene chloride, dimethylformamide-water (1:1), 10% trientlyharniae-methylene chloride, dimethylformamidewater (1:1), methanol, tetrahydrofuran and methanol. Subsequently, it was dried under reduced pressure to obtain 18.83 g (1.17 mmol/g) of a reside compound (1) shown in the above floure.

(2) A mixture comprising 16.73 g of the resin compound obtained in the above (1), 8.50 g of (S)-1-bromoacetyl-2-cyanopyrrolidine, 8.82 ml of diisopropylethylamine, and 80 ml of dimethylformamide was stirred at 50°C for 18 hours. The resin was collected by filtration, and washed with dimethylformamide, 10% triethylamine-methylene chloride, dimethylformamide-water (1:1), methanol, tetrallydrofuran and methanol. Subsequently, it was dried under reduced pressure to obtain 19.14 g (1.02 mmol/g) of a resin compound (2) shown in the above figure.

Reference Example 4

[0149]

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Reference Example 4

Boc: tert-butoxycarbonyl group Q: polystyrene residue

[0150] To 250 ml of an ethanol solution containing 30,00 g of 1.4-trans-cyclohexane diamine and 131 ml of 2N hydrochloric acid was added dropwise over 4 hours 150 ml of an ethanol solution containing 52,13 g of di-tert-buryl-dicarbonate under ice-cooling. The reaction mixture was stirred for 20 hours, concentrated and fulled with an acquesitific acid solution. It was then washed with chloroform and made alkaline by an aqueous sodium hydroxice solution. The solution was extracted with chloroform, dried, and concentrated to obtain 22,33 g of N-tert-butoxycarbonyl-trans-1,4-cyclohexanediamine.

[0151] Using this compound and a resin ((4-formyl-3,5-climathoxyphenyloxy)methyl polystyrene), the resin compound shown in the above figure was obtained in the same manner as mentioned above Reference Example 3 (1) and (2).

Reference Example 5

Boe: tert-butox yearbonyl gro Q: polystyrene residue

(1) 200 ml of a dioxane-water (1:1) solution containing 10.0 g of trans-4-aminomethyloyolohexanecarboxylic acid, 18 g of di-tert-butyldicationate and 11.2 g of sodium bicarbonate was strend at room temperature for 72 hours. To the reaction mixture were added 60 ml of an aqueous 10% NaOH solution and 300 ml of either, and an organic phase was separated. Subsequently, an aqueous phase was made acid by an aqueous 10% HCI solution, and axtracted with orthyl acidac. The axtract was washed with bind, eride over anhyforus sodium sulfate, and the solvent was removed under reduced pressure. The residue was washed with isopropyl other to obtain 15.3 g of trans-4-(tert-butoxycarbony)-aminomethylycylohexanecarboxylic acid.

(2) After 100 ml of a tolurene solution containing 5.15 g of the compound obtained in the above (1), 6.05 g of dipheny/phosphory) acide and 3.1 ml of triethylamine was refluxed for 3 hours, 2.3 ml of benzyl alcohol was added thereto and the mixture was further refluxed overnight. After cooling, the reaction mixture was concentrated, and the residue was purified by silica gel flesh column chromatography (solvent: ethyl acetate-chioroform (1.20)), and crystallized from hexane to obtain 5.32 g of N-benzyloxycarbony trans-4-(tert-butoxycarbonylaminomethyl)cyclohexylamine.

(3) 200 ml of an ethanol solution containing 5.19 g of the compound obtained in the above (2) and 10% palladium-carbon was stirred under hydrogen atmosphere at 1 atm for 6 hours.

The cetalyst was removed by filtration and the filtrate was washed with ethanol. The filtrate and the washing solution were combined. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (solvent: chloroloom-melhanol-concentrated aqueous ammonia (50 10:1)) and crystalized from a mixed solvent of isopropyl either-hoxane to obtain 2.55 g of trans-4-(tert-butoxycaronylaminomo-thyloxolobaxycamine.

(4) A mixture comprising the compound obtained in the above (3) (2.54 g), 4.15 g (1.43 mmo/g) of a rasin (14-formyl-35-dimethoxylophenyloxylinethyl polystyrens, 2.24 g of a solumi triaceloxyloprohydrids and 80 ml of methylene chorde was stirred at room tamperature for 20 hours. The resin was collected by filtration, and washed with methylene chloride, dimethylformamide, methylene chloride, 10% triethylarnine-methylene chloride, methylene chloride, methylene chloride, methylformamide, dimethylformamide, dimethylformamide, dimethylformamide, dimethylformamide, methanol, studentylformamide, dimethylformamide, methanol, studentylformamide, methanol, studentylformamide, methanol, studentylformamide, dimethylformamide, methanol, studentylformamide, methanol, studentylformamide,

(6) A mixture comprising 5.12 g (1.14 mmol/g) of the resin obtained in the above (4), 2.63 g of (S)-1-bromoacelyi-2-eyunopyrrolidine, 2.08 ml of disopropylethylarnine and 50 ml of dimethylformamide was stirred at 50 °C for 18 hours. The resin was collected by litration, and weshed with dimethylformamide, dimethylformamide water (1.11), dimethylformamide, methanol, letrahydrofuran, methanol, letrahydrofuran and methanol. Subsequently, it was dried under reduced pressure to obtain 6.78 g (1.01 mmol/g) of a resin compound (5) shown in the above fiture.

Reference Example 6-1

[0152]

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(1) According to the process described in the literature (JP83-118577), methyl 1,4-dioxaspiro[4.5]decan 8-carbox, ylate was reacted with methyl foldide in the presence of LDA (lithium discpropylamide) to obtain methyl 8-methyl-1,4-dioxaspiro[4.5]decan-8-carboxylate (the compound (1), of the above figure). (The starting material was synthesized according to the processes described in the literature by Resement of et al. (Chem. Ber., 1975, Vol. 108, pp. 1871-1895) and the Utrasturo by Black et al. (Synthesis, 1981, p. 829).)

(2) A mixture compraising 3.80 g of the compound obtained in the above (1), 3.55 g of anothum hydroxide, 16 m., of mothanol and 25 m., of water var entured for 2 hours. The reaction mixture was toe cooled, adjusted to pH is 9; 2N hydrochloric acid and an aqueous 10% cliric acid solution, and extracted with ethyl acetus. The extract was washed with water and brine, dried over arthydrous sodium suffate and the softward was removed under reduced pressure to obtain 3.46 g of 8 -methyl-1,4-dioxespiroid-5,blocar-6-acidoxylic acid (the compound (2) of the above

(3) A mixture comprising 16.19 g of the compound obtained in the above (2), 24.61 g of diphonylphosphonyl azide, 9.00 g of iridity/amine and 160 mL of bulene was refluxed for 2.5 hours. The reaction mixture was ce-cooled, washed with an equeous saturated sodium hydrogencurbonate solution, water and brine, and dried over anthytrous sodium suifate. Subsequently, the solvent was removed under reduced pressure 3.65 g of potaesium tert-butoxide was slowly added to 100 mL of a dimethylacetamide solution containing the resulting compound under ice cooling, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice-water, and the precipitated crystal was collected by filtration, washed with water and dried, To 100 mL of a tetrahydrofuran solution containing the resulting compound was added 100 mL of an aqueous solution containing 50.87 g of proluenesulfonic each hydrate, and the mixture was stirred at room temperature for 1 hours. The mixture was diluted with an aqueous saturated socium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dired over anhydrous sodium sulface, and the solvent was removed under reduced pressure to obtain 10.41 g of 4-tert-butoxycarbonylamine-4-methylcyclohexanone (the compound (3) of the above france).

(4) A mixture comprising 10.41 g of the compound obtained in the above (3), 11.01 g of sodium triacetoxyborohydride, 5.10 m.L of benzylamine and 15 om.L of methylene chloride was stirred at room temperature for 18 hours. The mixture was difuted with an aqueous saturated sodium hydrogencarbonate solution and extracted with eithy acetate. The extract was washed with water and brine, dried over anhydrous sodium suitate and the solvent was removed under reduced pressure. To 15 m.L of a methanol solution containing the resulting compound were added 3.32 g of p-toluenesulfonic acid, followed by 160 mL of ether. The presipitates were collected by filtration, weshed with other and dried to obtain 7.49 g of N-benzyl-t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexy-amine p-toluenesulfonic acid the compound (4) of the above floure).

(5) A nixture comprising 16.63 g of the compound obtained in the above (4), 5.0 g of 10% palladium-carbon and 400 mL of methanol was stirred under hydrogen atmosphere (1 atm) for 24 hours. 10% palladium-carbon was removed by filtration and the filtrate was concentrated. The resulting residue was dissolved in a mixture of 50 nL of an aqueous 10% sodium hydroxide solution and 300 mL of either. The ether layer was washed with water and brine, dried over anhydrous sodium suitate and the solvent was removed under reduced pressure to obtain 6.87 g of 14-41eth-butoxycarbonylamino-4-methyti-1-cyclohexylamile (the compound (5) of the above ficure).

(6) The filtrate in the step of the above (4) was treated with an aqueous socium hydroxide solution and extracted with chloroform. The extract was washed with water and brine, died over anhydrous socium suitete and the solvent was removed under reduced pressure. The reduction was expelled to Nt-ellies ago column chromatography (selvent hexane-eithyl acetate (30:1 to 3:1)) to obtain N-benzyl-c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexy-lamine. Next, this compound was treated in the same manner as mentioned above (5) to obtain c-4-tert-butoxy-carbonylamino-4-methyl-r-1-cyclohexylamino-4-methyl-r-1-cyclohexylamino-4-methyl-r-1-cyclohexylamino-4-tert-butoxy-carbonylamino-4-methyl-1-cyclohexylamine (file compound (6) of the above figure).

Reference Example 6-2

[0153] t-4-tert-Butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohoxylamine or c-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohoxylamine as in Reference 6-1 (1) to (5) or (5) except for using benzyloxymethyl-diodid in place of methyl iodide in the step of Reference Example 6-1 (1).

[0154] Also, 1-4-ten-butoxycarbonylamino-4-methoxymethyl-r1-cyclohexylamine or c-4-tent-butoxycarbonylamino-4-methoxymethyl-r1-cyclohexylamine was obtained in the same manner as Reference Example 6-1, (1) to (3) or (6) except for using methoxymethyl chloride in place of methyl icidide in the step of Reference Example 6-1, (1) or (6)

50 Reference Example 6-3

[0155]

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(1) N fart Butoxycarbonyl-4-carboxyl-4-methoxymathyl-piporidine was obtained by using N-tort-butoxycarbonyl-4-ethoxycarbonyl-iperidine (synthesized according to a method described in a literature of Giltigan et al. (J. Mec. Chem., Vol. 37, pp. 364-370, 1984)) and methoxymethyl chlorde in the same manner as in Reference Example 6-1 (1), followed by the same manner as in Reference Example 6-1 (2).

N-tert-butoxycarbonyl-4-benzyloxycarbonylamino-4-methoxymethylpiperidine was obtained in the same man-

ner as in Reference Example 6-1 (3) except for using this compound and further using benzyl alcohol in place of potassium tert-butoxide.

(2) A mixture comprising 9.4 g of the compound obtained in the above (1), 1.9 g of 10% palladium-carbon, and 190 mL of methanol was stirred under hydrogen atmosphere (1 atm) for 2 hours. 10% palladium-carbon was removed by filtratlot and the filtrate was concentrated to obtain 6.02 g of 4-amino-N-lert-butoxycarbonyl-4-methoxymethyligendine.

[0156] Subsequently, this compound was treated with an acid to remove a protective group (tert-butoxycarbonyl group) to obtain 4-amino-4-methoxymethylpiperidine.

Reference Example 6-4

[0157] A mixture comprising 3.78 g of N-tert-butoxycarbonyl-4-benzyloxycarbonylamino-4-methoxymethylpiperidine (a compound obtained in Reference Example 6-3 (1)) and 38 ml of concentrated hydrochloric acid was refluxed for 3 days. The reaction mixture was concentrated and the residue was washed with tetrahydrofuran to obtain 2.8 g of 4-mino-4-hydroxymethylpipendine dihydrochloride.

Reference Examples 7-1 to 7-7

20 [0158]

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(1) 18.7 ml of triethy amine was added to 200 ml of a totrahydrofuran solution containing 16 g of 4-amino-1-terbutoxycarbony piperidine and 17.5 g of N-carboethoxy-phthalmide under loe-cooling, and the mixture was stirred at room temperature for 4 hours. Water was added to the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with an equeous saturated sodium bloarborate solution, water and brine, dried over arhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was auspended in either-inexane, and crystals were collected by filtration to obtain 25.7 g of 2-(1-tert-butoxycarbonyl-scipled)-1-3-dione.

A 170 ml of 15% hydrochloric acid-ethanol suspension containing 25.5 g of this compound was stirred at room temperature for 5 hours. Precipitates were collected by filtration to obtain 18.0 g of 2-(4-pipericyl)iso:ndolin-1,3-dione hydrochloride.

(2) 3.13 ml of trightylamine was acided to 15 ml of tetre-hydrofuran-3 ml of N,N-dimethylacetamine solution containing 1.57 g of the compound obtained in the above (1) and 644 mg of 2-chloropyrimidine, and the mixture was stirred at 50°C for 12 hours. After cooling, an aqueous saturated sodium bicardonate solution was actied to the mixture, and the resulting mixture was extracted with othyl acotate. The extract was washed with water and brine, dried over anhydrous sodium euilde, and the solvent was removed under recticed pressure. The residue was suspended in ether-hexane, and crystals were collected by filtration to obtain 1.50 g of 2-(1-(2-pyrimidinyl)-4-pp-erityl)isolnoidin-1.3-dione. (vijetić 57%)

Subsequently, 0.26 ml of hydrazine-monohydrate was added to 16 ml of an ethanol suspension containing 800 mg of this compound and the mixture was refluxed for 2 hours. After cooling, insoluble products were removed by filtration and the solvent was removed under reduced pressure. The residue was purified by N+ silica gell itsals column chromatography (solvent:chloroform-methanol (500:1)) to obtain 417 mg of 4-amino-1-(2-pyrimidinyl);pip-eridine (heforence Example 7-1 in Table 9).

45 [0159] Also, compounds of Reference Examples 7-2 to 7-7 in Table 9 were obtained in the same manner as mentioned above by using the corresponding starting materials.

Beference Examples 8-1 to 8-7

[0160] 2 ml of an ethanoi suspension containing 260 mg of 4-amino-4-methylipiperidine (synthesized according to a method described in US.5821240), 237 mg of 2-chloropyrimidine and 858 mg of potassium carbonate was stirred at 50°C for 12 hours. The reaction mixture was poured into water, and extracted with horborform. The extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silicing of itlanio-dumon chromatography (solvent: chloroform-methanol-aquoous ammonia (300:10:1)] to obtain 259 mg of 4-amino-4-methyl-Nic2-privindinylopiednian (Federence Example 8-1 in Table 9).

[0161] Also, compounds of Reference Examples 8-2 to 8-7 in Table 9 were obtained in the same manner as mentioned above by using the corresponding starting materials.

Reference Examples 8-8 to 8-21

[0162] Compounds of Reference Examples 8-8 to 8-15 in Table 9 were obtained in the same manner as mentioned above-mentioned Reference Example 8-1, using 4-amino-4-methoxy-methylpiperidine (Reference Example 6-3 (2)) and corresponding starting materials.

[0163] Also, compounds of Reference Examples 8-16 to 8-21 in Table 9 were obtained in the same manner as mentioned above by using 4-amino-4-hydroxymethylpiperidine/dihydrochloride (Reference Example 6-4) and corresponding starting materials.

10 Reference Examples 8-22 to 8-23

[0164] 0.88 ml of trichylamine was added to 15 ml of a tetrahydrofuran suspension containing 1.00 g of 1.4-tert-butoxycarbonylamine-4-hydroxymethyl-1-t-yclohexylamine (Reference Example 6.2) and 897 mg of N-carboethoxyphthal-imide, and the mixture was heated at 50°C for 5 hours. Water was added to the reaction mixture, and the mixture was extracted with either and the mixture was extracted with either and the properties of the solution and brine, and dired over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain 1.47 g of N-tert-butoxycarbonyl-1-hydroxymethyl-1-4-phthalimide-1-cyclohexylamine. To a solution of 1.44 g of this compound in 10 ml of dloxane was added 10 ml of 4N hydrochloric add/dloxane, and the mixture was stirred at room temporature for 3 hours. The reaction mixture was diluted with diethyl either and crystals were collected by filtration. The obtained crystals were washed with diethyl either to obtain 1.03 g of 1-hydroxymethyl-1-4-phthalimide-1-cyclohexylamine (Reference Example 8.22 in Table 9).

[0165] Also, a compound of Reference Example 8-23 in Table 9 was obtained in the same manner as mentioned above.

25 Reference Example 8-24

[0166]

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(1) 15 mi of toluene-1.5 ml of chloroform solution containing 500 mg of N-tert-butoxycarbonyl-trans-1,4-cyclohex-ane-diamine, 623 mg of eithyl 2-bromomethyl benzoets and 354 mg of triethylamine was heated at 100°C for 5 hours. After cooling, water was added to the mixture and the resulting mixture was extracted with eithyl aceitate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silicing gel flash column chromatography to obtain 400 mg of N-tert-butoxycrophyt-trans-4(1-ove-2-isandiem)ylcyclohexylamine.

(2) 10 ml of 4N HCV/doxane was added to 10 ml of a dioxane solution containing 380 mg of the compound obtained in the above (1), and the mixture was etirred at room temperature for 5 hours. After the reaction mixture was concentrated, the residue was inturated with diethyl ether to obtain 298 mg of trans-4-(1-oxo-2-isoindolinyi)cyclohexyiamine hydrochloride (Reference Example 8-24 in Table 9).

40 Reference Examples 8-25 to 8-31

[0167] 15 ml of a chloroform solution containing 500 mg of N-tent-butoxycarbonyl-trans-1,4-cyclohexanediamine and 540 mg of 3-nitrophthatic antrydrios was added to the mixture and the resulting mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture and the resulting mixture was extracted with chloroform. The organic layer was washed with brine, dired over anhydrous addition suitate, and the solvent twas removed under reduced pressure. The residue was purified by select selection with the control of the solvent was removed under reduced pressure. The residue was purified by select selection of the control of the control

[0168] 10 ml of 4N HCl/dioxane solution was added to 10 ml of a dioxane suspension containing 885 mg of this of compound, and the mixture was stirred at room temperature for 5 hours. After the reaction mixture was concentrated, the residue was triturated with diethyl either to obtain 700 mg of trans-4-{1,3-dioxo-4-nitro-2-isoindolinyi)cyclohexyl-amine-hydrochlorids (Reference Example 8-25 in Table 9).

[0169] Also, compounds of Reference Examples 8-26 to 8-31 in Table 9 were obtained in the same manner by using the corresponding starting materials.

Reference Example 8-32

[0170] 1.49 ml of triethylamine was added to 20 ml of a methylene chloride solution containing 1.5 g of trimellitic

anhydride chloride and 0.303 ml of methanol under ice-cooling, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction mixture and the resulting mixture was extracted with chloroform. The organic layer was dried over anhydrous additin suitate and the solvent was removed under reduced pressure to obtain 19 g of 4-methoxycarbonylphthalic anhydride. Using this compound as a starting material in place of 3-nitrophthalic anhydride, trans 4-(1,3-dloxo-5-methoxycarbonyl2-iso-indolinyl)cyclohoxylamine hydrochloride (Reference Example 8-32 n Table) 9 was obtained in the same manner as in Reference Example 8-32 n Table) 9 was obtained in the same manner as in Reference Example 8-32.

Reference Examples 8-33 and 8-34

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[0171] To 10 ml of a methylene chloride solution containing 1.0 g of trimelitic arrhydride chloride were added \$54 mg of pyrrolidien and \$57 mg of trieflylenine under ice-cooling, and the mixture was attirred at room temperature for 2 hours. Water was added to the reaction mixture and the resulting mixture was extracted with chloroform. The organic layer was dried over arrhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain 1.09 g of 4-(1-pyrrolidinyl)parchorythrialic arrhydride. Using this compound as a starting material in place of 5-nitrophthalic arrhydride, trans-4-[1.3-dioxo-5-(1-pyroli-dinyl)carbonyl-2-solnodinyl(pyclohexylamine hydrochloride (Reference Example 8-25.

[0172] Also, a compound of Reference Example 8-34 in Table 9 was obtained in the same manner as described above. Reference Example 8-35

- (1) 5.92 ml of thionyl chloride was added to 150 ml of a methylene chloride suspension containing 15.00 g of trans-(4-benzyloxycarbonylamino)cyclohexan-1-carboxylic acid, and the mixture was refluxed for 4 hours. The reaction mixture was concentrated under reduced pressure, and by repeating an operation of adding methylene chloride and concentrating the mixture under reduced pressure for 2 times, trans-4-(benzyloxycarbonylamino) cyclohexanecarboxylic acid chloride was obtained.
- 25 (2) The compound obtained in the above (1) was dissolved in 70 ml of methylene chloride to make a solution, and added dropwise thereto was an aqueous solution comprising 60 ml of conc. aqueous ammonia-120 ml of water under ice-cooling. The mixture was stirred at room temperature for 50 minutes, and the resulting precipitates were collected by filtration. The precipitates were washed with water, 2 propanol, and isopropyl other to obtain 14-17 g of trans-4-(eparyl-vocyatrophysiam)ch devolute/succeptowarnide.
 - (3) 5.54 m lof thingry chloride was added to 140 m lof an acotonitrie suspension containing 7.00 g of the compound obtained in the above (2), and the mixture was refluxed for 30 minutes. The reaction mixture was concentrated undor reduced pressure, and after addition of acotonitrile, it was further concentrated under reduced pressure. Discopropy either was added to the obtained residual solid, and the solid was collected by flitration to obtain 6.14 g of trans-4/benzyloxyacotonylamino)-1-cyclohexaneachonitrile
 - (4) Hydrogen chiefde gas was fed into 24 mil of an ethanol suspension containing 1.20 g of the compound obtained in the above (3) under Ice-east cooling until the starting material was once dissolved, and then, procipitates came out again. This reaction mixture was stirred at room temperature for 14 hours, and concentrated under reduced pressure. To the obtained residue was added an equeous saturated sodium hydrogencarbonate solution, and then, the mixture was extracted with chioroform wikee. The extract was diffed over anhydrous solution suifate, and concentrated under reduced pressure to obtain 0.93 g of ethyl trans-4-(benzyloxycarbonylamino)cyclohexane-1-imidinate.
 - (5) 163 mg of ammonium chloride was added to a solution of 6 ml of ethanoi-1 ml of water containing 929 mg of the compound obtained in the above (4) and the mixture was stirred at room temperature for 9 hours. The reaction mixture was concentrated under reduced pressure, and an operation of adding toluene and concentrating the mixture under reduced pressure was repeated two times. To the obtained residual solid was added 0.3 ml of ethanoi-20 ml of either, and the solid was collected by filtration to obtain 859 mg of trans-4-(benzyloxycarbonylaminoi-1-cycle-hoxynecarboxyarian-no
 - (6) Using the compound obtained in the above (5) (500 mg) as a starting material, by reacting the same with ethoxyethylene malenonitrile according to the method of Schmidt, et al. (Schmidt, H. W. et al., J. Hetrocyel Chern, Vol. 24, p. 1305, 1987), trans-1-(cenzyloxycarbonylamino)-4-(4-amino-5-cyanopyrimidin-2-yl)cyclohexane (186 mg) was obtained
 - (7) 282 µl of trimethylsily iddde was added to a suspension of 174 mg of the compound obtained in the above (8) in 7 ml of an acetonitrile under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Ice-coil water was added to the reaction mixture and the mixture was washed with chloroform. Subsequently, potassium carbonate was added to the aqueous layer to saturate the mixture, and it was extracted with chloroform 3 times. The extracts were dried over anhydrous sodium suiffate and concentrated under reduced pressure to obtain 105 mg of trans-4-f-4-mino-5-venopyrinding-a-vytochexyulamine (Reference Example 8.5 in Table 9).

Reference Example 8-36

[0173] Using trans-4-(benzyloxycarbonylamino)-1-cyclohexane-carboxamidine/hydrochloride (a compound of Reference Example 8-35 (5)) (348 mg) as a starting material, by reacting the same with acetylacetone according to the method of Libran et al. (J. Chem. Soc., p. 2050, 1952), trans-1-benzyloxycarbonylamino-4-4/8-dimathlylyrimidin-2-ylloyclohexane (220 mg) was obtained. By treating this compound (205 mg) with trimethylsilyl lodide in the same manner as in Fletference Example 8-35 (7), trans-4-(4.5-dimathylpyrimidin-2-ylloyclohexylamine (Reference Example 8-36 in Table 9) (1729 mg) was obtained.

Reference Examples 8-37 to 8-39

[0174] A mixture comprising 500 mg of N-tert-butoxycarbonyl-trans-1,4-cyclobxanodismine, 226 mg of 1,4-dichiprobutane, 865 mg of potassium carbonale, 70 mg of sodium ioldie and ethanot-water (8 ml 2-m) was stirred at 97°C for 12 days. Water was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The extract was washed with brine, dided over anitydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The obtained residue was purified by slicing gel flash column chromatography (solvent: chloroform-methanolaqueous ammonia = 100:5/0.5 to 100:10/10.5) to obtain 453 mg of N-tert-butoxycarbonyl trans-4-(1-pyrroidinyl)cyclobexyl-aminor.

[0175] This compound was subjected to a deprotecting treatment under acidic conditions to obtain trans-4-(1-pyrrolidinyl)cyclohexylamine (Reference Example 8-37 in Table 9).

[0176] Also, compounds of Reference Examples 8-38 to 8-39 in Table 9 were obtained in the same manner as mentioned above.

Reference Example 8-40

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[0177] A mixture comprising 10 g of trans-4-(tert-butoxy-carbonylamino)cytolohexanecarboxylic acid, 7,8 g of 2-chio-ro-8-aminopylidine, 0.2 g of 1-6-di-emethylamino-propyl)s-dihylambota propolidine, and 180 mL of N.N-dimothyllormamida was stirred at room temperature for 15 hours. To the reaction mixturo was added an aqueous sodium hydrogen-carbonate solution to make the solution alkaline, and extracted with ethyl acotate. The extract was washed with water and brine, dride over enhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain trans-4-tert-butoxycarbonylamino-N-(2-chloro-3-pyridyl)-cyclohexanecar-boxanide.

Reference Example 8-41

[0178] A mixture comprising 500 mg of trans-4-fort-butoxy-carbonylamino-N-(2-ohloro-3-pyridy)(eyclohexanecerboxamide (Reference Example 8-40), 858 mg of 2,4-bls(4-methoxy-phenyl)-1,3-dithio-2,4-diphosphetane-2,4-disuffice and 10 mL of tetrahydrofuran was stirred at 60°C for 18 hours. Insoluble materials were removed by fittration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel flash column chromatourspity (solvent: chlorodim-methanol 50-1).

(9179) The obtained drude crystais were suspended in 5 mL, of ethenol and 10 mL of 4N-hydrochloric adid-ethenol solution was added to the suspension, and the mixture was refluxed for 1.5 hours, Ethanol was removed under reduced pressure and the resulting residue was dissolved in water and washed with ether. Potassium carbonate was added to the equeous layer to make the solution atkatine, and the solution was extracted with chloroform. The extract was washed with water and princ, dride over anhydrous sodium sultate, and the solvent was removed under reduced pressure to obtain 195 mg of trans-4-(thinzrioi(5,4-b)pyridin-2-yi)cyclohexyl-amine (Reference Example 8-41 in Table 9).

Reference Example 8-42

[0180] By treating trans-4-(benzyloxycarbonylamino)cydo-hexanecarboxylic acid and 2-aminophenol in the same manner as in Reference Example 8-40, trans-4-benzyloxycarbonyl-amino-N-(2-hydroxyphenyl)cyclohoxanecarboxamidie was obtained.

[0181] A mixture comprising 300 mg of this compound, 286 mg of pydidinium-p-toluenesulfonate, 6 mL of methanol, and 6 mL of 1.2-dichioromethane was refluxed for 48 hours. To the reaction mixture was added water and ethyl acetate, and the organic layer was separated. The extract was washed with brine, dried over anhydrous scdium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica get flash column chromatography (solvent: chilorofrom).

[0182] A mixture comprising 150 mg of this compound, 30 mg of 10% palladium-carbon and 7.5 mL of methanol was stirred under hydrogen atmosphere (at 1 atm) at room temperature for 2 hours. The catalyst was removed by filtration and the filtrate was concentrated to obtain 63 mg of trans-4-(benzo[d][1,3]oxazol-2-yl)cyclohexylamine (Reference Example 9-42 in Table 9).

Reference Example 8-43

[0183]

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(1) In 35 ml of tetrahydrofuran was suspended 0.74 g of sodium boron hydride, and boron trifluoride dicthyl complex was added to the suspension under loc cooling. The nativue was stirred as such under loc cooling for 30 minutes, and 90 ml of a totrahydrofuran solution containing 3.60 g of trans-4-(barry/syarabny/amino/sychokaxenaer-boxylic acid was added thereto under loe cooling. After the mixture was stirred at room temperature for 2 hours, the reaction mixture was pound into an ice water and extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the scivent was removed under reduced pressure. The residue was suspended in disopropyl other and collected by filtration to obtain N-benzyloxycerbonyl-trans-4-(hydroxymothy/leyolchexylamine).

(2) 0.81 mil of oxalyl chloride was added to 95 ml of a dichloromethane solution containing 1.95 g of the compound obtained in the above (1) and 1.45 g of dimethylsulfoxide at .78°C. The mixture was stirred at .45°C for 2 hours, and then, it was cooled down to .78°C. To the mixture was added 5 ml of a dichloromethane solution containing 5.82 g of triethylamine, and after clevating the temperature to room temperature, the mixture was stirred for 2 hours. The reaction mixture was washed with water, hydrochloric acid solution and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (solvent: hexane-athyl acetate = 4.1) to obtain trans-4-(benzyloxy-carbonylamino)cyclonexane-

(g) To a solution of 512 µL of thionyl chloride in 4 mL of dichloromethene was added dropwise a solution of 586 µL of pyridine in 4 mL of dichloromethane, under loc-cooling. Subsequently, 1,53 g of the compound obtained in the above (2) was added thereto. The resction mixture was stirred at room temperature for 1 hour, and added thereto were 715 mg of 2-aminobanylamine, followed by a solution of 15 mL of water containing 981 mg of sodium acetate. After the reaction mixture was stirred at room temperature for 1 hour, dichloromethane was removed under reduced pressure. To the residual mixture was added an aqueous 10%-sodium hydroxide solution to make the mixture alkaline, and it was stirred at room temperature for 10% sodium hydroxide solution to make the mixture alkaline, and it was stirred at room temperature for 30 minutes, and the solvent was removed under reduced pressure. A mixture comprising the obtained redelike 2, 65 g of 2,3 dichloro-5,8-dicyano-1,4-benz oquinone and 75 mL of toluene was stirred at room temperature for 14 hours. The reaction mixture was diluted with chieroform and successively weeked with an aqueous 10%-sodium hydroxide solution, vater and brine, crited over anythrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silice gel flash column chromatography (solvent: chloroform). The obtained residue was further suspended in a mixed solvent of losporacy lefther-hexane, and the resulting precipitates were collected by fillerather.

[0184] In 7 mL of acetonitrile was dissolved 362 mg of this compound. Under ice-cooling, 427 µL of trimethylsilyl lodide was added dropwise thereto, and the mixture was stirred at room temperature for 15 minutes. To the reaction mixture were added mothand and water, and the was washed with choroform. The expression was added potable and and vater, and the was washed with choroform. The extract was washed with water and brine, died over anthydrous sodium validate, and it was extracted with chloroform. The extract was washed with water and brine, died over anthydrous sodium validate, and the solvent was removed under reduced pressure to obtain 220 mg of trans-4-duniazoling-24/bothoxyvalmine (Reference Example 8-3) in Table 8-3.

Reference Example 8-44

0 [0185] Trans-4-(benzyloxycarbonylamino)cyclohoxanacarboxylic acid and 3- (aninomethylcarbonyl)pyridine were treated in the same manner as mentioned above Reference Example 8-40 to obtain trans-4-benzyloxycarbonylamino-N-(3-pyridyl-carbonylmethyl)cyclohoxanocarboxamide.

[0186] A mixture comprising 600 mg of this compound, 283 µL of phosphorous oxychioride and 9 m L of Nh. Admethylform-amide was sitred at room temperature for 1 hour. The reaction mixture was poured into water, and after the mixture was made alkaline by adding an aqueous sodium bicarbonario solution, it was extracted with sthyl acelste. The extract was washed with water and brinc, dired over anhydrous sodium suitate, and the solvent was removed under reduced prossure. The residue was suspended in diethyl either, and the resulting precipitates were collected by fittation.

[0187] A mixture comprising 350 mg of this compound, 70 mg of 10% palladium-carbon and 17.5 mL of methanol was stirred under hydrogen atmosphere (1 atm) at room temperature for 20 hours. The catalyst was removed by filtration and the filtrate was concentrated to obtain 211 mg of trans-4-[5-(3-pyridyl)-1,3-oxazol-2-yl]cyclohexylamine. (Reference Example 6-44 in Table 9).

Reference Examples 8-45 to 8-56

[0188] 4-tert-butoxycarbonylamino-4-methylcyclohexanone (the compound (3) of Reference Example 6-1) and corresponding starting materials (amine compounds) were stirred in the presence of sodium triacetoxyborohydride at room temperature for 16 hours for reaction to proceed. Subsequently, an acid treatment was carried out for removing the protective group (t-butoxycarbonyl group) to obtain compounds of Reference Examples 4-45 to 8-58 in Table 9.

Reference Examples 8-57 to 8-59.

(188) 418 mg of sodium trlacetoxyborchydride was added to a solution of 300 mg of 1-4-tert-butoxycarbonylamino-4-methyl-r1-cyclohexylamine (a compound oblained in the above Afference Example 6-1 (5)) dissolved in a mixed solvent of 2 mf of tertarylydrivan and 0.5 mf of formalin, and the mixture was stirred at room temperature for 16 hours. An aquecus 10% sodium hydroxide solution was added thereto and the mixture was extracted with chloroform, and dried over anhydrous sodium suffate. The solvent was removed under reduced pressure and the residue was purified by siliace after loolution chromatography (solvent: chloroform-methenol-aqueous ammonis (65)-15 to 10:10.11

[0190] This compound was stirred in 2 mt of 4N hydrochloric acid-dioxane, and 2 mt of ethanol for 8 hours, and then, the reaction mixture was concentrated. An aqueous 10% sodium hydroxide solution was added thereto. The mixture was extracted with chloroform, dried over anhydrous sodium sulfate, and the solvent was removed under rectade pressure to obtain 55 mg of t-4-dimethylamino-1-methyl-1-1-cyclo-bexysimine (Reference Example 8-57 in Table 9). [0191] Similarly, compounds of Heference Examples 8-58 to 8-59 in Table 9 were obtained.

Reference Examples 9-1 to 9-3

[0192] To 10 ml of a methylene chloride solution containing 1.04 g of triphosgene were added 10 ml of a methylene chloride solution containing 1.59 g of N-ethoxycerbonyl-piperazine and 1.4 ml of triethylamine under ice-cooling, and the mixture was siltered as such for 15 minutes.

[0193] To the mixture was added 10 ml of a methylene chloride solution containing 1.00 g of 4-tert-butoxycarbonylaminopipendine and 0.77 ml of triethylamine under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into an ice water and extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent; ethyl accetate:hexane = 4:1) to obtain 0.94 g of 4-tertbutoxycarbonylamino-1-(4-chroxycarbonyl-1-piperazinyl)carbonyloiperidine.

[0194] In 8 ml of methylene chloride was dissolved 0.66 g of this compound, and 2 ml of Influoroacelic acid was added thereto, and the mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue was purified by N1 silica gel flash column chromatography (solvent; chloroform: methanol = 100:1) to obtain 0.42 g of 4-amlno-1-(4-ethoxycarbonyi-1-piperaziny)(carbonylpiperidine (Reference Example 9-1 in Table 10)

[0195] Also, by using 4-tert-butoxycarbonylaminopiperidine and corresponding starting materials, compounds of Reference Examples 9-2 and 9-3 were obtained in the same manner as mentioned above.

Reference Examples 9-4 and 9-5

[0196]

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(1) N-nitrocomethytures was added cropwise to a suspension comprising an aqueous potessium hydroxide solution (4 g of KCH/10 ml of water) and 27 ml of ether under ide-cooling. After completion of the dropwise addition, the other layer of the reaction mixture was separated and potassium hydroxide was added thereto, and the mixture was left in a refrigerator for 3 hours. To an after solution of this diazomethane was gradually added 2.00 g of trans-4-(bonzy)*coyacthorylamino(cyclohexane carboxylic addichloride (a compound obtained in Reference Example 8-35 (1)), and the mixture was stirred at room temperature for 2 hours. The resulting crystals were collected by filtration and weathed with other to obtain 1.63 g of N-benzylioyacthoryl-trans-4-(diazoacsyl-tipocyl-diazoacyt-tipocyl-diazoacyt-tipocyl-diazoacyt-tipocyl-diazoacyt-tipocyl-diazoacyt-tipocyt-tipocyt-tipocyt-diazoacyt-tipocyt-diazoacyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-tipocyt-

for 1 hour, and then, at 69°C for 30 mnutes. After the reaction mixture was cooled down to room temperature, water was added thereto and the mixture was extracted with ethyl, acetate. The extract was successively washed with water and brine, dred over annyticous sodium sulfate, and the solvent was removed under reduced pressure. The obtained residue was suspended in either and the resulting precipitates were collected by filtration to obtain 741 mg of N-bernydovyacathout Prians 4-4 (morthollinocarbon/wheth)—exploite/wildmine.

A suspension of 4 ml of methanol containing this compound (350 mg) and 70 mg of 10% palladium-carbon was stirred under hydrogen atmosphere at room temporature and at normal pressure for 3 hours. The catalyst was removed by litiration and the filtrate was concentrated to obtain trans-4-(morpholinocarbony/methyl)cyclohexylamine (Reforence Example 9-4 in Table 10).

(3) To 10 ml of a methylene chloride solution containing 1.00 g of the compound obtained in the above (1) was added 10 ml of 11 k hydrochiefo acet-either solution, and the mixture was eithred at room temperature for 4 hours. To the reaction mixture was added an aqueous saturated sodium bicarbonate solution and extracted with chloroform. The extract was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain N benzylovycarbonyt trans-4-(chloroacet/bycolhoxytlamine).

[0197] A mixture comprising this compound (400 mg), 1.12 g of morpholine and 6 m1 of methylene chloride was stirred at room temperature overnight. Mator was added to the reaction mixture and the resulting mixture was extracted with chloroform. The extract was successively washed with water and brine, died over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was suspended in either and resulting procipitates were collected by filterion to obtain 417 mg of N-benzyloxy-carbonyl-trans-4-(morpholinomethylcarbonyl)cyclohoxylamine. [0198] A suspension of 4 m1 of methanol containing this compound and 72 mg of 10% polladium-carbon was stirred under hydrogen antrosphere at room temperature and normal pressure for one hour. The catalyst was removed by filtra-tion and the filtrate was concentrated to obtain trans-4-(morpholinomethylcarbonyl)cyclohoxylamine (Reference Example 9.6 in Table 10).

Reference Examples 9-6 and 9-7

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[0199] Ethyl trans-4-aminocyclohexanecarboxylate hydrochloride (Reference Example 9-6) and othyl cis 4-aminocyclo-hexanecarboxylate-hydrochloride (Reference Example 9-7) were synthesized according to the method described of in a literature (Johnston et al. J. Med. Chem., 1971; Vol. 14, pp. 600-614, pp. 600-614).

Reference Examples 9-8 to 9-12

[0200] To 6 mL of a tetrahydrofuran solution containing 1.0 g of trans-4-(fert-butoxycarbornyiamino,byc)ohexanol and 873 mg of benzylbromide was graculally added 204 mg of 60%, sodium hydride, 0.5 mL of dimethyl suffoxide was then further added thereto, and the mixture was stirred at 70°C for 2 hours. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water and ohine, dried over anhydrous sodium suffate, and the solvent was removed unfor reduced pressure. The residure was applied to silica gel column chromatography (solvent: hoxane-ethyl acetate (4:1)), and the obtained powdery crysta's were suspended in an ethyl acetate-hexane mixed solvent; and collected by filtrafion to obtain farms-1-ter-butoxycerpomylemino-4-theproxycoxyce/obbexane.

[9201] To a suspension of this compound in ethanol was added 2N hydrochloric acid-dioxane solution, and the mixture was stirred at room temperature for 18 hours to offect deprotection to obtain trans-4-(benzyloxy)cyclohexylamine hydrochloride (Reference Example 9-8).

[0202] Also, by using corresponding starting materials, compounds of Reference Examples 9-9 to 9-12 in Table 10 were obtained in the same manner as mentioned above.

Reference Example 9-13

[0203] In 10 ml of methanol was dissolved 204 mg of N-tert-butoxycarbonyl-trans-4-(2-propen-1-yloxy)-cyclesy-ve-lamine (the compound of Reference Example 9-11). 44 mg of 10% paliadium-earbon was acided thereto, and the mixture was stirred under hydrogen atmosphere at normal pressure, at room temperature for 2 days. The catalyst was removed by filtration and the solvent was removed and the residue was stirred in 2 ml of trifluoroacelic acid for 3 hours. The solvent was removed, and the residue was mixed with an aqueues 10% caddium hydroxide solution, extracted with chioroform and dried over anhydrous sodium sutfate. The solvent was removed under reduced pressure to obtain 102 g mg of trans-4(cropox)/cyclobxylamine (Reference Example 9-13 in Table 10-9-13 in Table 10-8).

Reference Examples 9-14 to 9-29

[0204]

- 5 (1) 9.33 g of sodium boron hydride was suspended in 200 ml of tetrahydrofuran, and added thereto was, boron trifluoride diethy complex under loe-cooling. The mixture was stirred as such under loe-cooling for 30 minutes, and then, 150 ml of a tetrahydrofuran solution containing 40 g of trans4-cft-en-buoxycadronylam-nolycylorhexane carboxylic acid was added thereto under loe-cooling. The mixture was stirred at room temperature for 4 hours, and the reaction mixture was poured into ice water, and extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was corrystallized from ethyl acetate-hexane to obtain 20 g of N-tert-butoxy carbonyl-trans 4. (hydroxymothyl/cyclohoxylamine.)
 - (2) By using the compound obtained in the above (1) and corresponding starting materials, compounds of Reference Examples 9-14 to 9-29 in Table 10 were obtained in the same manner as in Reference Example 9-8.

Reference Examples 9-30 to 9-33

[0205]

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- (1) To a mothylene chloride suspension containing 5.00 g of trans-4-(text-butoxycerbony)aminolycyclohexanol were added 4.68 ml of tricthylamine and 3.09 g of methanesulfonyl chloride at 0°C, and the mixture was attired for 10 minutes. Water was added to the reaction mixture and the resulting mixture was extracted with orbyl acotate. The extract was washed with water, an aqueous saturated sodium bloarbonate solution and brine, dired over anhydrous sodium suitets, and the solvent was removed under reduced pressure. The residue was suspended in an ethyl acotate-isopropyl either mixed solvent, and collected by filtration to obtain 6.19 g of trans-4-tert-butoxycarbonylami-nocyclo-haxymethanes suitonate.
 - (2) 0.818 g of 60% sodium hydride was added to 10 ml of a dimethylformamide solution containing 2-mercaptopyridine-8-carbon/lifle under loc-cooling and the mixture was etirred at room temperature for 1 hour. Added thereto was 2.00 g of the compound obtained in the above (1), and the mixture was stirred at room temperature overnight, and at 80°C for 8 hours, and cooled down to room temperature. Water and ethyl acetate were added to the reaction mixture and the organic layer was separated. The extract was successively washed with an aqueous sodium hydroxide solution, water and brine, dited over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: othyl acetatehexane (158) to obtain 0.977 gol clei-1-teri-buxycarbonylamino-4(5-cyane-2-pyridythio(xol-c)-bxane.
- [0206] 0.977 g of this compound was dissolved in chioreform and 4 ml of 4N-hydrochlorio acid-dioxane solution was added thereic, and the mixture was attred at room temperature for 4 hours. To the reaction mixture was added a little amount of methanol to crystalize an objective compound, and the solvent was evaported to dryness. The residue was suspended in a mixed solvent of methanol:dilsopropyl either, and collected by filtration to obtain 0.787 g of cis-4-(5-cyano-2-pyridythilo)cyclobaxylamine (Afederonce Example 9-30 in Table 10 s.)

[0207] Also, by using corresponding starting materials, compounds of Reference Examples 9-31 to 9-33 in Table 10 were obtained in the same manner as mentioned above.

Reference Example 10-1

f02081

- (1) To a suspension in which 42.8 g of 5-hitroisoindoline had been added to an equeous potassium carbonate solution (108 g of potassium carbonate, 200 ml of water) was added dropwise 200 ml of an ethyl acetate solution containing 31 2 ml of chloroacetyl chlorida at 0°C over 1 nour The mixture was further stirred at 0°C for 45 minutes and precipitates were collected by filtration. The obtained solid was treated with activated carbon in ethyl acetate and recrystatiged to obtain 2-6-hioroacetyl-5-mixtosi-indoline.
- (2) In 10 ml of NN-dimathy/formamide were stirred 1.21 g of the compound obtained in the above (1), 1.07 g of N 1 ort outoxycarbonyl trans-1,4-cyclohexanddiamine and 1.39 g of polassium carbonate at room temporature for 20 hours. The reaction mixture was pound into water and precipitates dolles were collected by filtration, weshed with water, dried, and purified by silica gel column chromatography (solvent, chloroform-methanol-98:2 to 95.5) to ootain N-tent-butoxycarbonyl-varis-4-(f5-nitro-2-isoindolinyl)-authonylmethylmemiolycyclohoxylamine. In 3 ml of trifluoroacetic acid was dissolved 246 mg of this compound and the solution was stirred at room temporature for

2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was made basic by 10% sodium hydroxide and extracted with chloroform. The extract was dried over anhydrous sodium surfate and concentrated under reduced pressure to obtain trans-4-{6-nitro-2-isoindolinyi)carbon-ylmethylamino|cyclohexy-lamine (Reference Example 10-1 in Table 11).

Beference Examples 10-2 to 10-13

[0209] 10 ml of a NN-dimethylicomamide solution containing 1 g of N4ert-butoxycarbonyl-trans-1, 4-cyclohaxanediamine, 832 mg of 3-pyridinearboxylic acid, 1 of g of 1-sthylis-(3-dimethylaminopropyl)-carbodimids and 757 mg of 1-hydroxybenzofriazole was stirred at room temperature for 24 hours. To the reaction mixture was added an aqueous saturated sodium hydrogenearbonate solution and the resulting mixture was extracted with eithyl acetiate. The extract was washed with brine, dried over anhydrous acidum, sulfate, and the solvent was removed under reduced pressure. The residue was vessed with distribly ather to obtain N-tert-butoxycarbonyl-trans-4,4-pyridylcarbonyl-aminolycioloxyl-amino. A mixture comprising 1.27 g of this compound and 13 mil of 15 hydrochloria acid-ethanics lostic was stirred at 6°0°C to 2 hours. After cooling, precipitates were filtered and washed with diethyl ether to obtain 1.12 g of trans-4,6-pyridylcarbonylaminolycycholoxylamine dilydycorboride (Reference, Example 10.2 in Table 11).

[0210] Also, by using corresponding starting materials, compounds of Reference Examples 10-3 and 10-4 in Table 11 were obtained in the same manner.

[0211] Also, by using t- or c-4-tert-butoxycarbonylamine-4-methyl-r-1-cyclohexylamine (the compound of Reference Example 6-1 (5) or (6)) and corresponding starting materials, compounds of Reference Examples 10-5 to 10-10 in Table 11 were obtained in the same manner. (Provided that the formed hydrochloride was converted into a free form by treating with an aqueous potassium carbonate solution.)

[0212] Also, by using t- or c-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohexylamine (Reference Example 6-2) and corresponding starting materials, compounds of Reference Examples 10-11 to 10-13 in Table 11 were obtained in the same manner.

Reference Examples 10-14 to 10-17

[0213]

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(1) To 160 ml of a methylene chloride solution containing 16.83 g of 4-(tert-butoxycatbonylarmino)cyclobaxanone and 10.55 ml of N-methylbenzytamine was added 10.88 g of solut misacetoxyochydride under loce-cooling, and the mixture was stirred at the omtemperature for 14 hours. The reaction mixture was diluted with an aqueous sodium hydrogenearbonate solution and extracted with eithyl acetate. The extract was washed with water and brief do over anhydrous sodium suffate and the schent was removed under reduced pressure. The obtained residue was supended in hexane and collected by litration. This mother liquor was concentrated and the residue was purified by NH-eillacg glichromatography (solven): hexane-ethyl acetate (8-73.6 83:17). The residue was further supended in hexane and collected by litration and combined with the filtered product to obtain 15.55 g of Ni-benzyl-Ni-teributoxy-carbonyl-Ni-methyl-trans-1,4-cyclobaxanoidamine.

A suspension of 13,53 g of this compound and 2,00 g of palladium hydroxide-carbon in methanol was subjected to catalytic hydrogenation under normal pressure and at room temperature over 5 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to obtain 9,93 g of N-tert-butoxycarbonyl-N'-methyl-trans-1,4-cyclohexanediamine.

(2) A mixture comprising 500 mg of the compound obtained in the above (1), 326 mg of 2-pyrazinearboxylic acid, 355 mg of 1-pyrazinearboxylic acid, 355 mg of 1-pyrazinearboxylic mixture was a compression of 10 mg of 1

[0214] The obtained residue was suspended in disappropyl ether, and collected by filtration to obtain N-tert-butoxy-carbonyl-N'-methyl-N'-(2-pyrazinylcarbonyl)-trans-1,4-cyclohexanediamine.

[0216] Subsequently, 420 mg of this compound was dissolved in 6 ml of dioxane, then, 5 ml of 4N hydrochloric aciddioxane was added thereto, and the mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with ether, and the resulting precipitates were collected by filtration, and washed with ether to obtain powder. A solution of the obtained powder dissolved in water was saturated with potassium carbonate, and extracted with chloroform. The oxtract was dried over anthydrous sedium suitled and the solvent was removed under reduced pressure

to obtain N-methyl-N-(2-pyrazinylcarbonyl)-trans-1,4-cyclohexanodiamine (Reference Example 10-14 in Table 11). [0216] Also, by using the compound obtained in the above (1) and corresponding starting materials (carboxylic acid compounds), compounds of Reference Examples 10-15 to 10-17 in Table 11 were obtained in the same manner as mentioned above.

Beference Examples 10-18 to 10-20

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[0217] 254 µ l of methanesulfonyl chloride was added to a methylene chloride solution containing 500 mg of N-tentbutoxycarbonyl-N-methyl-trans.1.4-eyclohoxarodarianie (Relearence Example 10-14 (1)) and 758 µ of triethylane, and the mixture was affired at room temperature for 14 hours. To the reaction mixture were added water, followed by an equeous saturated sodium hydrogenearbonate solution, and the mixture was extracted with othyl acetate. The extract was washed with an aqueous saturated sodium hydrogenearbonate, water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The obtained residue was suspended in dischexpropyl eiter, and collected by filtration to obtain N-tert-buloxycarbonyl-N-methyl-N-methylsulfonyl-trans-1,4-cyclohoxaned lamine. Subsequently, fils compound was treaded with hydrochloric acid to obtain N-methyl-N-methyl-sulfonyltrans-1,4-cyclohoxarandiamine (Releterece Example 10-18 in Table 11).

[0218] Also, by using corresponding starting materials (chlorides), compounds of Reference Examples 10-19 and 10-20 in Table 11 were obtained in the same manner as mentioned above.

[0219] in the following Table 1 to Table 11, chemical structures and physical properties of the compounds of the above Examples and Reference Examples are shown. (In these Tables, "Mr 'represents methyl group. Also, in the Tables, MS-APCI (m/z) represents values from mass spectrometry (atmospheric pressure chemical ionization mass spectrometry).)

| 1.1 | | T | able | 1 | |
|----------------|----------------------|-----|----------------|------|---|
| ** . | R ² -X-B | | R ¹ | NC' | \mathcal{D} |
| Example No. | R2-X- | В | R ¹ | Salt | Physical properties, etc. |
| 1-1 | ∠ _N | N | Н | 2HC1 | Colorless powder MS APCI(m/z): 315 [M+H]+ |
| 1-2 | Br \(\bigcirc_N \) | N | Н | 2HC1 | Colorless powder MS APCI(m/z): 499 [M+H]+ |
| 1-3 | CI- | N | Н | 2HC1 | Colorless powder MS APCI(m/z): 349 [M+H]+ |
| 1-4 | 0 ₂ N-{_N | . N | н | 2HC1 | Pale yellowish powder MS-APCI(m/z): 359 [M+H]+ |
| 1-5 | ис-С | N | н | 2HC1 | Colorless powder MS APCI(m/z): 339 [M+H]+ |
| 1-6 | NO ₂ | N | H | 2HCl | Yellowish powder MS APCI(m/z): 359 [M+H]+ |
| 1-7 . | CN CN | N | Н | 2HC1 | Colorless powder MS APCI(m/z): 339 [M+H]+ |
| 1-8 | NC-CN | N | Me | 2HCl | Colorless powder MS_APCI(m/z): 353 [M+H]+ |
| . 1-9 | O_2N | N | Me | 2НС1 | Yellowish powder MS·APCI(m/z): 373 [M+H]+ |
| 1-10 | CN | N | Ме | 2HC1 | Colorless powder MS APCI(m/z): 353 [M+H]+ |

Table 1 (Continued)

| | 1a | pre | I (Cont. | inuea) | |
|-------------|--------------------|-----|---------------------|---------|--|
| | R ² -X- | -в | R ¹ | | Ď |
| Example No. | R²-X- | В | R ¹ | NC Salt | Physical properties, etc. |
| 1-11 | NO ₂ | N | Me | 2HC1 | Yellowish powder MS APCI(m/z): 329 [M+H]+ |
| 1-12 | | N | Me | 2HC1 | Colorless powder MS·APCI(m/z): 329 [M+H]+ |
| 1-13 | Br- | N | Me | 2HC1 | Colorless powder MS APCI(m/z): 407, 409 [N+H]+ |
| 1-14 | N N | N | Ме | 2HC1 | Yellowish powder MS APCI(m/z): 329 [M+H]+ |
| 1-15 | 0 ₂ N-{ | N | CH ₂ OMe | 2HC1 | Yellowish powder MS APCI(m/z): 403 [M+H]+ |
| 1-16 | NC- | N | CH ₂ OMe | 2HCl | Colorless powder MS APCI(m/z): 383 [M+H]+ |
| 1-17 | NO ₂ | N | CH ₂ OMe | 2HC1 | Yellowish powder MS APCI(m/z): 403 [M+H]+ |
| 1-18 | CN CN | N | CH ₂ OMe | 2HC1 | Colorless powder MS-APCI(m/z): 383 [M+H]+ |
| 1-19 | N N | N | CH ₂ OMe | 2HC1 | Colorless powder MS APCI(m/z) r 359 [M+H]+ |
| 1-20 | | N | CH ₂ OMe | 2HC1 | Yellowish powder MS APCI(m/z): 359 [M+H]+ |
| 1-21 | CI N-N | N | CH ₂ OMe | 2HC1 | Colorless powder MS·APCI(m/z): 393 [M+H]+ |

Table 1 (Continued)

| a , | R ² -X- | В | R ¹ | P _N | γ |
|----------------|----------------------|----|---------------------|----------------|---|
| | | | | NC | |
| Example No. | R ² -X- | В | R ¹ | Salt | Physical properties, et |
| 1-22 | N-N | N | CH ₂ OMe | 2HC1 | Yellowish powde MS APCI (m/z): 3 [M+H]+ |
| 1-23 | NC- | N | CH ₂ OH | 2HCl | Colorless powds MS APCI (m/z): 3 [M+H]+ |
| 1-24 | | N | СН₂ОН | 2HC1 | Colorless powds MS APCI(m/z): 3 [M+H]+ |
| 1-25 | N- | N | CH ₂ OH | 2HC1 | Yellowish powde MS APCI(m/z): 3 [M+H]+ |
| 1-26 | 0 ₂ N-{ | N | СН₂ОН | 2HC1 | Yellowish powde MS APCI(m/z): 3 [M+H]+ |
| 1-27 | CN CN | N | Сн₂ОН | 2HC1 | Colorless powde MS APCI(m/z): 3 [M+H]+ |
| 1-28 | $\bigvee_{N}^{NO_2}$ | N | СН₂ОН | 2HC1 | Yellowish powde MS·APCI(m/z): 3 [M+H]+ |
| 1-29 | Nie | СН | Н | HC1 | Colorless powde MS APCI(m/z): 3 [M+H]+ |
| 1-30 | Nhi | СН | н | HC1 | Colorless powde MS APCI(m/z): 3 [M+H]+ |

Table 1 (Continued)

| | | | | IIIųeu) | |
|----------------|--|----|----------------|---------|---|
| | R^2-X-B | | l H ■N | | |
| | | | | NC | |
| Example No. | R²-X- | В | R ¹ | Salt | Physical properties, etc. |
| 1-31 | NO ₂ | СН | Н | HC1 | Colorless powder MS APCI(m/z): 426 [M+H]+ |
| 1-32 | CH ₃ | CH | H | HC1 | Colorless powder MS APCI(m/z): 395 [M+H]+ |
| 1-33 | | СН | Н | 2HC1 | Colorless powder MS APCI(m/z): 382 [M+H]+ |
| 1-34 | | CH | H | HC1 | Colorless powder MS APCI(m/z): 333 (M+H]+ |
| 1-35 | | CH | ·H | HC1 | Colorless powder MS APCI(m/z): 444 [M+H]+ |
| 1-36 | | CH | Н | HC1 | Colorless powder MS APCI(m/z): 482 (M+H]+ |
| 1-37 | H.C.O. | CH | H | HC1 | Colorless powder MS APCI (m/z): 406" [M+H]+ |
| 1-38 | H ₃ C ₁ , I H _{Nii} . | СН | Н | HC1 | Colorless powder MS APCI(m/z): 439 [M+H]+ |
| 1-39 | | СН | H | HCI | Colorless powder MS APCI(m/z): 478 [M+H]+ |

Table 1 (Continued)

| | | | 1., | | , | |
|---|----------------|---------------------------------------|--------|--------------------------|------|--|
| | | R ² -X-B | | R ¹ H N | | $\hat{\gamma}$ |
| 1 | | | | | NC | . 1% |
| | Example No. | R ² -X- | В | R¹. | Salt | Physical properties, etc. |
| | 1-40 | | СН | H | HCl | Colorless powder MS APCI (m/z): 492 [M+H]+ |
| | 1-41 | NC NC | СН | н . | 2HC1 | Colorless powder MS APCI(m/z): 354 [M+H]+ |
| | 1-42 | H ₃ C N | СН | н | HCl | Colorless powder MS APCI(m/z): 342 [M+H]+ |
| | 1-43 | Nimm | CH | H | 2HC1 | Colorless powder MS APCI(m/z): 305 [M+H] |
| | 1-44 | O_Nim- | CH | ijĤ | 2HC1 | Colorless powder MS APCI(m/z): 321 -{M+H |
| | 1-45 | Nie Nie | CH . | H . | 2HC1 | Colorless powder MS-APCI(m/z): 353 [M+H] |
| | 1-46 | N S | СН | Н | 2HCl | Purified powder MS APCI(m/z): 370 [M+H]+ |
| | 1-47 | N Inc. | СН | Ħ | HCl | Purified powder MS·APCI(m/z): 353 [M+H]+ |
| | 1-48 | N N | CH | H | 2HC1 | Purified powder MS APCI(m/z): 364 [M+H]+ |
| | 1-49 | N N N N N N N N N N N N N N N N N N N | СН | H | 2HCl | Purified powder MS APCI(m/z): 380 [M+H]+ |

Table 1 (Continued)

| 1-50 O CH CH ₂ OH HC1 Clolorless powder MS APCI (m/z): 411 (M+H)+ 1-51 N CH Me 2HC1 Colorless powder MS APCI (m/z): 31 (M+H)+ 1-52 NC NW CH Me 2HC1 Purified powder MS APCI (m/z): 30 1-53 H ₃ C-O H ₃ C CH Me 2HC1 Purified powder MS APCI (m/z): 30 1-54 H ₃ C H ₃ C CH Me 2HC1 Purified powder MS APCI (m/z): 32 1-55 CH ₃ CH Me 2HC1 Purified powder MS APCI (m/z): 32 1-56 CH ₃ CH Me 2HC1 Purified powder MS APCI (m/z): 32 1-57 CH Me 3HC1 Purified powder MS APCI (m/z): 32 1-58 H ₃ C CH Me 3HC1 Colorless powder MS APCI (m/z): 38 [M+H] 1-58 N H HC1 Colorless purified powder MS APCI (m/z): 42 COlorless purified powder MS APCI (m/z): 42 1-59 N H HC1 Colorless purified powder MS APCI (m/z): 42 | | Table | T (C | contin | ued) | |
|---|------|-----------------------|-----------|----------------|---------|---|
| No. | | R ² -X-B | - Millian | | O NC | ĵ. |
| NIP | | R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
| N | 1-50 | Nille | СН | СН₂ОН | HC1 | |
| NC N | 1-51 | | СН | Ме | 2HC1 | |
| 1-54 H ₃ C N ₁ M ₁ CH Me 2HC1 Purified powder MS APCI (m/z): 29 1-55 CH ₃ CH H ₃ C N ₁ M ₂ CH Me 2HC1 Purified powder MS APCI (m/z): 30 1-56 CH ₃ CH Me 2HC1 Purified powder MS APCI (m/z): 30 1-57 CH Me 3HC1 Colorless powder MS APCI (m/z): 38 (M+H)+ 1-58 N H ₃ C N H H HC1 Colorless purified powder MS APCI (m/z): 42 1-59 N H HC1 Colorless purified powder MS APCI (m/z): 42 1-59 N H HC1 Colorless purified powder MS APCI (m/z): 38 APCI (m/z): 42 1-59 N H HC1 Colorless purified powder MS APCI (m/z): 38 APCI (m/z): 32 1-59 N H HC1 Colorless purified powder MS APCI (m/z): 32 APCI (m/z): 32 APCI (m/z): 32 APCI (m/z): 32 APCI (m/z): 35 | 1-52 | . н | СН | Ме | 2HC1 | Purified powder MS APCI(m/z): 304 |
| H ₃ C N MS APCI (m/z): 29 | 1-53 | Nilo | СН | Me | 2HC1 | Purified powder MS APCI(m/z): 381 |
| H ₃ C H ₃ CH Me 2HCl (m/z): 30 1-56 H ₃ C CH Me 2HCl Purified powder MS APCl (m/z): 32 1-57 CH Me 3HCl Colorless powder MS APCl (m/z): 38 [M+H]+ 1-58 H ₃ C ON N H HCl Colorless purific powder MS APCl (m/z): 42: 1-59 N H HCl Colorless purific powder MS APCl (m/z): 35 [N H HCl Colorless purific powder MS APCl (m/z): 35] | 1-54 | H ₃ C Nim. | СН | Me | 2HC1 | MS APCI(m/z): 293 |
| 1-57 H ₃ C H ₄ CH Me 3HCl Colorless powder MS APCI (m/z): 32 -58 CH ₃ N H HCl Colorless purific powder MS APCI (m/z): 42: 42: 42: 45: 45: 45: 45: 45: 45: 45: 45: 45: 45 | 1-55 | H.C. NIII | CH | Me | 2HC1 | Purified powder MS APCI(m/z): 307 |
| 1-58 | 1-56 | | СН | Me | 2HCl | Purified powder MS APCI(m/z): 321 |
| powder MS APCI (m/z): 42: 1-59 N H HC1 Colorless purific powder NS APCI (m/z): 35(| 1-57 | | CH | Me | ЭНС1 | Colorless powder MS APCI(m/z): 384 [M+H]+ |
| o N powder ms APCI (m/z): 35(| 1-58 | H,c O N | N | Н | HC1 | Colorless purified powder MS APCI(m/z): 421 |
| | 1-59 | | N | н . | HC1 | Colorless purified powder MS APCI(m/z): 350 |

| | R ² -X-B | | R ¹ H N | O N | \bigcirc |
|---------|------------------------|-----|--------------------------|------|---|
| Example | | T. | · | NC | Physical |
| No. | R²-X- | В | R ¹ | Salt | properties, etc. |
| 1-60 | H ₃ C N | . N | H | HC1 | Colorless purified powder MS APCI(m/z): 308 |
| 1-61 | ON I mm | СН | Н | HCl | Colorless powder MS APCI(m/z): 363 [M+H] |
| 1-62 | ° On √lam. | CH | . н | 2нС1 | Colorless powder MS APCI(m/z): 363 [M+H] |
| 1-63 | H ₃ C O | CH | н | HC1 | Colorless powder MS APCI(m/z): 308 [M+H]+ |
| 1-64 | H₃C O | СН | Н | HC1 | Colorless powder MS·APCI(m/z): 308 [M+H]+ |
| 1-65 | O om. | СН | н | HC1 | Purified powder MS APCI(m/z): 342 |
| 1-66 | H³C- ^{O///} . | СН | H | HC1 | Purified powder MS·APCI(m/z): 266 |
| 1-67 | H³C Ohn. | СН | Н | HC1 | Purified powder MS APCI(m/z): 280 |
| 1-68 | H ₂ C Oliv | СН | н | HC1 | Purified powder MS APCI(m/z): 292 |

Table 1 (Continued)

| | | - 1 | | | | | |
|----|-----|----------------|--------------------------|---------|---------------------|----------------------|---|
| 5 | | - | R ² -X-B | | R¹ F H ■N, |) | |
| 10 | | Example No. | R²-X- | В | R ¹ | NC Salt | Physical properties, etc. |
| 15 | | 1-69 | H³C O Om. | CH . | Н | HCl | Purified powder MS APCI(m/z): 310 |
| | | 1-70 | H³C Ollin. | CH | Н | HC1 | Purified powder MS APCI(m/z): 294 |
| 20 | | 1-71 | NO ₂ | CH | H | 2HC1 | Colorless purified powder MS APCI(m/z): 388 |
| 25 | . ! | 1-72 | 02N N O M. | CH | н | 2HC1 | Colorless purified powder MS APCI(m/z): 388 |
| 30 | | 1-73 | CN CN | CH | H | 2HC1 | Colorless purified powder MS APCI(m/z): 368 |
| | | 1-74 | NC (N) O MI | CH · | н | 2HC1 | Colorless purified powder MS APCI(m/z): 368 |
| 35 | | 1-75 | E N O WW. | СН | Н | HC1 | Colorless purified powder MS APCI(m/z): 412 |
| 40 | | 1-76 | (N) O mm | CH | н | HC1 | Colorless purified powder MS APCI(m/z): 344 |
| | | 1-77 | (N) CI | CH | н | HC1 | Colorless purified powder MS APCI(m/z): 378 |
| 45 | Ĭ - | 1-78 | F CN | СН | Н | HCl | Colorless purified powder MS-APCI(m/z): 385 |
| 50 | | 1-79 | H ₃ C-OCN OCN | СН | Н | HC1 | Colorless purified powder MS APCI(m/z): 397 |
| 56 | | 1-80 | CN O MI | СН | Н | HC1 | Colorless purified powder MS·APCI(m/z): 401 |
| | | | | | | | |

| | Table | - | | nued) | |
|---------------|------------------------|----------|----------------|---------|--|
| | R ² -X-B | Rational | H N | O NC | $\hat{\mathcal{L}}$ |
| xample No. | R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
| 1-81 | CN O Num | CH | H | HC1 | Colorless purified powder MS APCI(m/z): 381 |
| 1-82 | CN O Min | . CH | Н | HC1 | Colorless purified powder MS APCI(m/z): 367 |
| 1-83 | NC O Min. | СН | Н | HC1 | Colorless purified powder MS APCI(m/z): 367 |
| 1-84 | NO ₂ | СН | H | HC1 | Colorless purified powder MS APCI(m/z): 387 |
| 1-85 | 02N 0 Mm | СН | Н | HC1 | Colorless purified powder MS APCI(m/z): 387 |
| .1-86 | Br N | СН | . Н | HC1 | Colorless purified powder MS APCI(m/z): 423 |
| 1-87 | 0 ₂ N-{_N-s | СН | н | HC1 | Pale yellowish powder MS APCI (m/z): 390 [M+H]+ |
| 1-88 | F F S | CH | H | HC1 | Colorless powder MS APCI(m/z): 413 [M+H]+ |
| 1-89 | NC-S-S | CH | Н | HCl | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 1-90 | cı—S—s | СН | Н | HC1 | Colorless powder MS·APCI(m/z): 378 [M+H]+ |

| | Table | | | inea, | 1 |
|----------------|---------------------------------------|----|---------------|-------|---|
| 1. | R^2-X-B | R | ¹ ■H N~ | | |
| | | | | NC | |
| Example No. | R2-X- | В | R1 | Salt | Physical properties, etc |
| 1-91 | Cn Lum | СН | H | 2HC1 | Purified powder MS APCI(m/z): 387 [M+H]+ |
| 1-92 | O'N CON LIM | СН | Н | 2HCl | Colorless powde MS APCI(m/z): 455 [M+H]+ |
| 1-93 | H'C-OO Bum | СН | Н | 2HC1 | Colorless powde: MS APCI(m/z): 414 [M+H]+ |
| 1-94 | N Nu. | СН | Ме | 2HC1 | Colorless powde MS APCI(m/z): 370 [M+H]+ |
| 1-95 | N N N N N N N N N N N N N N N N N N N | СН | Me | 2HC1 | Colorless powde: MS APCI(m/z): 370 [M+H]+ |
| 1-96 | N O N | СН | Me | 2HC1 | Colorless powder MS APCI(m/z): 371 [M+H]+ |
| 1-97 | €N N N | СН | Me | 2HC1 | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 1-98 | N N N | СН | Me | 2HC1 | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 1-99 | N L | CH | Ме | 2HC1 | Colorless powder MS APCI(m/z): 371 [M+H]+ |

| | Table | 21 (| Continu | ıed) | |
|----------------|---------------------------------------|------|---------------------------|-------|---|
| | R ² -X-B | > | R ¹ H ■N | NC NC | > |
| Example No. | R ² -X- | В | R ^L | Salt | Physical properties, etc. |
| 1-100 | N N N N N N N N N N N N N N N N N N N | СН | СН₂ОН | 2HC1 | Colorless powder MS APCI(m/z): 386 [M+H]+ |
| 1-101 | N N N | СН | CH ₂ OH | HC1 | Colorless powder MS APCI(m/z): 387 [M+H]+ |
| 1-102 | O ₂ N O N N | CH. | СН₂ОН | HC1 | Colorless powder MS APCI(m/z): 420 [M+H]+ |
| 1-103 | N O CH ₃ | CH | Н | 2HC1 | Purified powder MS APCI(m/z): 371 [M+H]+ |
| 1-104 | N CH3 | СН | Н | 2HC1 | Purified powder. MS APCI(m/z): 370 [M+H]+ |
| 1-105 | N O CH ₃ | СН | Ħ | 2HCl | Furified powder MS APCI(m/z): 370 [M+H]+ |
| 1-106 | ON NHI | CH | H | 2HC1 | Unpurified powder MS APCI(m/z): 406 [M+H]+ |
| 1~107 | ON LH3 | CH | н | HC1 | Purified powder MS APCI(m/z); 378 [M+H]+ |

Table 1 (Continued)

| | * | | | | |
|----------------|--|----|--------------|---------|--|
| | R²−X−₽ | | R' H N | O NC | |
| Example No. | R2-X- | В | R1 | Salt | Physical properties, etc. |
| 1-108 | H ₃ C — S — N'''' O CH ₃ | СН | H | HC1 | Purified powder MS APCI(m/z): 343 [M+H]+ |
| 1-109 | H ₃ C \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | СН | Н | HC1 | Purified powder MS APCI(m/z): 419 [M+H]+ |

| | | ± | | le 2 | | , 8 |
|-----|----------------|----------------------------------|------|-------------------|-------|---------------------------------------|
| | | R ² -X-B | | Z¹ H N N | NC NC | \supset |
| | Example No. | R ² -X- | В | R ¹ . | Salt | Physical properties, etc. |
| | 2-1 | o N► | CH | Ме | 2HC1 | Purified powder MS APCI(m/z): 335 |
| | 2-2 | O NIIII | CH | Ме | 2HC1 | Purified powder MS APCI(m/z): 335 |
| | 2-3 | H ₃ C Nilia | ·CH | Me | 2HC1 | Purified powder MS APCI (m/z): 376 |
| | 2-4 | H ₃ C N Nille | СН | Me | 2HCl | Purified powder MS APCI(m/z): 390 |
| | 2-5 | H ₃ C CH ₃ | СН | Ме | 2HC1 | Purified powder MS APCI(m/z): 404 |
| - 1 | 2-6 | H ₃ C N Nie | CH | Me | 2HC1 | Purified powder MS APCI(m/z): 418 |
| | . 2-7 | NHIII. | . CH | Ме | SHC1 | Purified powder MS APCI(m/z): 402 |
| | 2-8 | N _N | CH . | Me | 2HC1 | Purified powder MS APCI(m/z): 444 |
| | 2-9 | N Nille | СН | Ме | 2HCl | Purified powder MS APCI(m/z): 410 |

| 5 | | | Ta | ble 3 | * . | | Ť |
|----|----------------|----------|-----------|------------------|-------|---|---|
| 10 | | R²-X—В́ | \supset | R' H N | NC NC | > | |
| | Example No. | R2-X | В | . R ¹ | Salt | Physical properties, etc. | |
| 15 | 3 | o Ni You | СН | H : | HC1 | Colorless crystal Melting point: 213°C- (decomposed) | |

| | R ² -X-B | Z Million | ¹ H N | O NC | |
|----------------|--|-----------|------------------------|---------|---|
| Example No. | R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
| 4-1 | OH | Ñ | Н | HC1 | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 4-2 | | N | Н | HC1 | Colorless powder MS APCI(m/z): 356 [M+H]+ |
| 4-3 | H,C \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | N | Н | HC1 | Colorless powder MS APCI(m/z): 336 [M+H]+ |
| 4-4 | но | N | Н. | HC1 | Colorless powder MS APCI(m/z): 337 [M+H]+ |
| 4-5 | HO | N . | Н | HC1 | Colorless powder MS APCI(m/z): 351 [M+H]+ |
| 4-6 | CH₃O | N. | Н | HC1 | Colorless powder MS APCI(m/z): 295 [M+H]+ |
| 4-7 | O V | ,N | H | HC1 | Colorless powder MS-APCI(m/z): 357 [M+H]+ |
| 4-8 | H ₃ C-\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | N | H | HCl | Colorless powder MS APCI(m/z): 391 [M+H]+ |
| 4-9 | О Н ₃ С-\$ | N | н | HC1 | Colorless crystal Melting point: 95-98°C |
| 4-10 | 0=%=0 | N | н | HCl | Brownish powder MS APCI(m/z): 403 [M+H]+ |

Table 4 (Continued)

| | 17 . 18 | | | | 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
|----------------|---------------------|--|----------|--------------|--|
| | R ² -X-B | - International Property of the Inte | H. H. | N NC | <u> </u> |
| Example No. | R ² -X- | В | R | Salt | Physical properties, etc. |
| 4-11 | | N | Н | 2HC1 | Colorless powder MS AFCI(m/z): 392 [M+H]+ |
| 4-12 | Of | N | H. | HC1 | Colorless powder MS APCI (m/z): 341 [M+H]+ |
| 4-13 | Br | N. | . н . | HC1 | Colorless powder MS APCI(m/z): 419 [M+H]+ |
| 4-14 | H ₂ N-S | N | Н | Free form | Colorless crystal Melting point: 135-140°C MS APCI (m/z): 420 [M+H]+ |
| 4-15 | | N | H | 2HC1 | Colorless powder MS APCI(m/z): 342 [M+H]+ |
| 4-16 | S | N | Н | HCl | Colorless powder MS APCI(m/z): 347 [M+H]+ |
| 4-17 | CH ₃ O | N | Н | HCl | Colorless powder MS APCI(m/z): 309 [M+H]+ |
| 4-18 | H ₃ C O | N | H | .,HCJ | Colorless powder MS APCI(m/z): 307 [M+H]+ |
| 4-19 | ° N~√√ | N | н | 2HC1 | Colorless powder MS APCI (m/z): 378 [M+H]+ |

Table 5

| | - | | | | | |
|-----|------|--------------------------|--------|---------|-------|---|
| | | R ² -X-B | Edimus | ■N N | NC NC | $\hat{\mathcal{T}}$ |
| | mple | R2-X- | В | R1 | Salt | Physical properties, etc. |
| 5 | -1 | | СН | Н | HC1 | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 5 | -2 | NC NC N N N | СН | Н | HC1 | Colorless powder MS APCI(m/z): 395 [M+H]+ |
| 5 | -3 | H,c~H L | CH | Н | HC1 | Colorless powder MS APCI(m/z): 350 [M+H]+ |
| . 5 | -4 | но Н | СН | H | HC1 | Colorless powder MS APCI (m/z): (ESI) 351 [M+H] |
| 5 | -5 | HO Nu. | СН | Н | HC1 | Brownish powder MS APCI(m/z): (ESI) 363 [M-H] |
| 5 | -6 | CH³O \ H _M , | СН | Н | HC1 | Colorless powder MS APCI(m/z): 309 [M+H]+ |
| 5 | -7 | Qol _{Min} | CH | Н | HC1 | Colorless powder MS APCI(m/z): 371 [M+H]+ |
| 5 | -8 | CH ₃ | СН | Н | HC1 | Colorless powder MS APCI(m/z): 384 [M+H]+ |
| 5- | -9 | H ₃ C O N NW. | СН | н | HC1 | Colorless powder MS-APCI(m/z): 322 [M+H]+ |
| 5~ | 10 | o N ↓ N, | СН | H | HC1 | Colorless powder MS APCI (m/z): 364 [M+H]+ |

Table 5 (Continued)

| | R ² -X-B | | H N | O N | \rightarrow |
|----------------|--|----|----------------|--------|---|
| | | _/ | | NC | - ∕ |
| Example No. | R ² -X- | B | R ¹ | Salt | Physical properties, etc. |
| 5-11 | H ₃ C - Num. | CH | H | HC1 | Brownish powder MS APCI(m/z): 405 [M+H]+ |
| 5-12 | H ₃ C-8 - N _{III} | СН | Н | HC1 | Brownish powder MS-APCI(m/z): 329 [M+H]+ |
| 5-13 | N _M , N _M , | CH | Н | 2HC1 | Colorless powder MS-APCI(m/z): 356 [M+H]+ |
| 5-14 | N N N | CH | , H | 2HC1. | Colorless powder MS APCI (m/z): 356 [M+H]+ |
| 5-15 | Br O N'III' | СН | н | 2HC1 | Colorless powder MS APCI (m/z): 434, 436[M+H]+ |
| . 5-16 | | CH | H | 2HC1 | Colorless powder MS·APCI(m/z): 390 [M+H]+ |
| 5-17 | $H^{3}N$ N N N N N N N N N | CH | Н . | 2HC1 | Colorless powder MS APCI(m/z): 371 [M+H]+ |
| 5-18 | N N N N N N N N N N N N N N N N N N N | СН | Н | HC1 | Pale yellowish powder MS APCI(m/z): 357 [M:H]+ |
| 5~19 | C P N | СН | H | 2HC1 | Colorless powder MS APCI(m/z): 406 [M+H]+ |
| 5-20 | S CH, H | СН | H | HC1 | Brownish powder MS APCI(m/z): 376 [M+H]+ |

Table 5 (Continued)

| | 16516 | | | iideu, | |
|----------------|------------------------|---------|----------------|---------|--|
| * | R ² —X—B | Rillini | H N |) No | \bigcirc |
| Example No. | R2-X- | В | R ¹ | NC Salt | Physical properties, etc. |
| 5-21 | H ₃ C N-N H | СН | H | HC1 | Colorless powder MS APCI(m/z): 401 [M+H]+ |
| 5-22 | H ₃ C N H | СН | Н | HC1 | Colorless powder MS APCI(m/z): 360 [M+H]+ |
| 5-23 | OCH ₁ ONW | CH | | HC1 | Colorless powder MS APCI (m/z): 415 [M+H]+ |
| 5-24 | D Nm. | СН | H | HC1 | Colorless powder MS APCI(m/z): 319 [M+H]+ |
| 5-25 | O I'm | СН | Н | HC1 | Colorless powder MS APCI(m/z): 437 [M+H]+ |
| 5-26 | N N N | CH | Н | 2HCl | Colorless powder MS APCI(m/z): 370 [M+H]+ |
| 5-27 | ○N N NW | CH | Н | 2HC1 | Colorless powder MS APCI(m/z): 376 [M+H]+ |
| 5-28 | | СН | Н | 2HC1 | Colorless powder MS APCI(m/z): 392 [M+H]+ |
| 5-29 | NH. | СН | Н . | HC1 | Colorless powder MS·APCI(m/z): 385 [M+H]+ |

Table 5 (Continued)

| | | | | | ., |
|----------------|--|----|----------|------|--|
| - | R ² -X-B | | ₹¹ ■N | L | |
| | _ | _ | | NC♥ | |
| Example No. | R2-X- | В | R1 | Salt | Physical properties, etc. |
| 5-30 | H³C | CH | н | HC1 | Colorless powder MS APCI(m/z): 293 [M+H]+ |
| 5-31 | NO NO NO. | CH | Н | 2HCl | Colorless amorphous MS APCI(m/z): 370 [M+H]+ |
| 5-32 | N N N N N N N N N N N N N N N N N N N | CH | н | 2HC1 | Colorless amorphous MS APCI(m/z): 370 [M+H]+ |
| 5-33 | S-CH ₃ | CH | Н | 2HC1 | Colorless amorphous MS APCI(m/z): 416 [M+H]+ |
| 5-34 | N N M | СН | н | HC1 | Colorless amorphous MS APCI(m/z): 371 [M+H]+ |
| 5-35 | 0 N-N N N N N N N N N N N N N N N N N N | CH | H | HC1 | Colorless amorphous MS APCI(m/z): 387 [M+H]+ |
| 5~36 | N O H | CH | Н | HCl | Colorless amorphous MS·APCI(m/z): 385 [M+H]+ |
| 5-37 | Br N H | CH | H | HCl | Colorless powder MS APCI(m/z): 421 [M+H]+ |
| 5-38 | O ₂ N-\(\bigc\) \(\bigc\) \(\bigc\) \(\bigc\) | СН | Н | 2HC1 | Colorless amorphous MS APCI(m/z): 387 [M+H]+ |
| 5-39 | NC-N-N-M- | СН | H | 2HC1 | Colorless amorphous MS-APCI(m/z): 367 [M+H]+ |

| | | | Tal | ble | 6 | ************************************** |
|----|----------------|-------------------------------|-----|----------------|--------|---|
| ." | | R ² —X—B | | R ¹ | I O NC | 1) |
| | Example No. | R ² -X- | • в | R ¹ | Salt | Physical properties, etc. |
| | 6-1 | CI- | CH | Н | 2HC1 | Colorless powder MS APCI(m/z): 377 [M+H)+ |
| | 6-2 | H _j C _s | СН | Н | 2HCl | Colorless powder MS APCI(m/z): 389 [M+H]+ |
| | 6-3 | | CH | H | 2HC1 | Colorless powder MS APCI(m/z): 343 [M+H]+ |
| - | 6-4 | NO2 | СН | н | 2HCl | Pale yellowish powder MS APCI(m/z): 387 [M+H]+ |

Table 7

| | | | EP 13 | 323 71 | 0 A1 | |
|---|----------------|-------------------------------------|-------|----------------|------|---|
| | | | | ble | 7 | 5. T. O |
| | | R²−X—В | | R ¹ | NC' | ∑ s |
| | Example No. | R2-X- | В | R1 | Salt | Physical properties, etc. |
| | 7-1 | , | N | H°. | 2HC1 | Colorless powder MS APCI(m/z): 333 [M+H]+ |
| | 7-2 | O ₂ N-{_N | N | Н | 2HC1 | Pale yellowish powder MS APCI(m/z): 377 [M+H]+ |
| , | 7-3 | NC- | N | Н | 2HC1 | Colorless powder MS APCI(m/z): 357 [M+H]+ |
| | 7-4 | $Br \stackrel{N}{\longleftarrow} N$ | N | н | 2HC1 | Colorless powder MS APCI(m/z): 411 [M+H]+ |
| | 7-5 | CI N | N | H | 2HC1 | Colorless powder MS APCI(m/z): 367 [M+H]+ |
| - | 7-6 | NC-(N | N | Me | 2HC1 | Colorless powder MS APCI(m/z): 371 [M+H]+ |
| | 7-7 | | N | Me | SHC1 | Colorless powder MS APCI (m/z): 347 [M+H]+ |
| | 7-8 | N H H | CH | H | 2HCl | Colorless powder MS APCI-(m/z): 374 [M+H]+ |
| | 7-9 | N H | СН | Н | 2HC1 | Colorless powder MS APCI(m/z): 374 [M+H]+ |
| | 7-10 | S CH' | СН | Н | 2HCl | Colorless powder MS APCI(m/z): 394 [M+H]+ |

Table 8

| | | | 31 | .: | |
|----------------|--|----|--------|-----------------|---|
| | R ² -X-B | | H N | JL _N | s |
| Example No. | R ² -X- | В | R1 | NC Salt | Physical |
| 8-1 | O_2N N N N N N N N N N | СН | Н | 2HC1 | properties, etc. Pale yellowish powder MS APCI(m/z): 405 [M+H]+ |
| 8-2 | NC-N-N-III | СН | Н | 2HC1 | Colorless powder MS·APCI(m/z): 385 [M+H]+ |
| 8-3 | Br-\(\bigc\)-H_m | CH | Н | 2HC1 | Colorless powder MS APCI(m/z): 439 [M+H]+ |
| 8-4 | CI-N-W-W | CH | Н | 2HC1 | Colorless powder MS-APCI(m/z): 395 [M+H]+ |
| 8-5 | H ₃ C N H | СН | Н | Free | Colorless powder MS APCI(m/z): 407 [M+H]+ |
| 8-6 | N H M | CH | Н. | 2HCl | Colorless powder MS APCI(m/z): 361 [M+H]+ |
| 8-7 | CN M | CH | H | 2HC1 | Colorless powder MS APCI(m/z): 388 [M+H]+ |
| 8-8 | N N N N N N N N N N N N N N N N N N N | СН | H | 2HC1 | Colorless powder MS·APCI(m/z): 388 [M+H]+ |

| | R ² - | -x-e | | R ¹ NH ₂ | |
|-----------------------------|-------------------|------|-----|-----------------------------------|--|
| Reference Example No. | R2-X- | В | R1. | Salt | Physical properties, etc. |
| 7-1 | | N | н | Free form | Colorless crystal Melting point: 76-79°C |
| 7-2 | 0 ₂ N- | N | Н | 2HC1 | Colorless crystal Melting point: 251-256°C |
| 7-3 | ис-С | N | H | Free form | Colorless crystal Melting point: 68-71°C |
| 7-4 | Br—N | N | Н | Free form | Colorless crystal Melting point: 113-115°C |
| 7-5 | CI— | N | Н | Free | Colorless crystal Melting point: 54-56°C |
| 7~6 | NO ₂ | N | H | Free form | Yellowish oil MS APCI(m/z): 223 [M+H]+ |
| 7-7 | | N | н | Free form | Colorless oil MS APCI(m/z): 203 [M+H]+ |

Table 9 (Continued)

| | | | ' | | |
|------------------------------|---|----|---------------------|-----------------------------------|---|
| | R | ²X | -в | R ¹ NH ₂ | |
| Referenc e Example No. | R2-X- | В | R ¹ | Salt | Physical properties, etc. |
| 8-1 | N N N N N N N N N N N N N | N. | Ме | Free form | Colorless liquid MS APCI (m/z): 19 [M+H]+ |
| 8-2 | NC NC | N | Me | form | Colorless powder MS APCI(m/z): 217 [M+H]+ |
| 8-3 | O ₂ N-\(\bigcirc_N\) | N | Me | Free . | Yellowish powder MS APCI(m/z): 237 [M+H]+ |
| 8-4- | CN CN | N | Me | Free form | Colorless liquid MS APCI(m/z): 217 [M+H]+ |
| 8-5 | NO ₂ | N | Me | Free form | Yellowish powder MS APCI(m/z): 237 [M+H]+ |
| 8-6 | Br— | Ņ | Me | Free form | Colorless powder MS APCI(m/z): 271 273 [M+H]+ |
| 8-7 | | N | Me. | Free form | Colorless powder MS APCI(m/z): 193 [M+H]+ |
| 8-8 | . O ₂ N— | N | CH ₂ OMe | Free form | Yellowish powder MS APCI(m/z): 26 [M+H]+ |
| 8-9 | NC- | N | CH ₂ OMe | Free form | Colorless powder MS APCI(m/z): 24 [M+H]+ |
| 8-10 | NO ₂ | N | CH ₂ CMe | Free form | Yellowish liquid MS·APCI(m/z): 26 [M+H]+ |
| 8-11 | ∑ ^{CN} | N | CH ₂ OMe | Free | Colorless liquid MS APCI(m/z): 247 [M+H]+ |

Table 9 (Continued)

| | Reference Example No. | R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
|-----|-----------------------------|--|----|---------------------|--------------|--|
| 10 | 8-12 | | N | CH ₂ OMe | Free form | Colorless liquid MS·APCI(m/z): 223 [M+H]+ |
| | 8-13 | _\ | N | CH ₂ OMe | Free form | Colorless liquid MS APCI(m/z): 223 [M+H]+ |
| 5 | 8-14 | √ √ √ √ √ √ √ √ √ √ √ √ √ √ √ √ √ √ √ | N | CH₂OMe | Free form | Colorless powder MS·APCI(m/z): 223 [M+H]+ |
| 10 | 8-15 | CI—(| И. | CH ₂ OMe | form | Colorless powder MS APCI(m/z): 257 [M+H]+ |
| | 8-16 | 0 ₂ N-\(\bigc\) | N | СН₂ОН | Free form | Yellowish powder MS APCI(m/z): 235 [M+H]+ |
| 25 | 8-17 | | N | СН₂ОН | free | Colorless oil MS APCI(m/z): 233 [M+H]+ |
| | 8-18 | NO ₂ | N | СН₂ОН | form- | Yellowish oil MS APCI(m/z): 253 [M+H]+ |
| 10 | 8-19 | NC- | N | CH ₂ OH | Free form | Colorless powder MS APCI(m/z): 233 [M+H]+ |
| s · | 8-20 | $\langle \rangle$ | N | СН₂ОН | Free form | Colorless powder MS APCI(m/z): 209 [M+H]+ |
| | 8-21 | | И٠ | CH ₂ OH | Free form | Colorless powder MS·APCI(m/z): 209 [M+H]+ |
| 0 | 8-22 | CK, | СН | СН₂ОН | HCl | Colorless solid Melting point: 265-267°C |
| 5 | 8-23 | Name of State of Stat | СН | Ĥ: | HC1 | Colorless solid Melting point: >300°C MS·APCI(m/z): 245 [M+H]+ |
| o | | | | | 2404 | |
| - | | | | | | |

Table 9 (Continued)

| | | 0.00 | | | | |
|------|-----------------------------|--------------------|----|----------------|------|---|
| | Reference Example No. | R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
| | 8-24 | NIII. | СН | - H | HC1 | Colorless solid MS APCI(m/z): 231 [M+H]+ |
| 1. | 8-25 | o, N N | СН | H . | HC1 | Colorless solid MS APCI(m/z): 290 [M+H]+ |
| - | 8-26 | CH; | CH | н | HC1 | Colorless solid MS APCI(m/z): 259 [M+H]+ |
| | 8-27 | N NIII | CH | Н | 2HC1 | Colorless solid MS APCI (m/z): 246 [M+H]+ |
| | 8-28 | Nitro | CH | ·H | HC1 | Colorless solid MS APCI(m/z): 197 [M+H]+ |
| | 8-29 | | CH | н | HCl | Colorless solid MS APCI(m/z): 308 [M+H]+ |
| | 8-30 | a grant | СН | н | HC1 | Colorless solid MS APCI(m/z): 346 [M+H]+ |
| | 8-31 | H,C-0 N | CH | н | HC1 | Colorless solid MS APCI(m/z): 270 [M+H]+ |
| ٠. [| 8-32 | н,с. | CH | н | HC1 | Colorless solid MS·APCI(m/z): 303 {M+H}+ |
| | 8-33 | | СН | н | HC1 | Colorless solid MS APCI(m/z): 342 [M+H]+ |

Table 9 (Continued)

| Reference Example No. | mple R ² -X- | В | R ¹ | Salt | Physical properties, etc. |
|-----------------------------|---------------------------|----|----------------|--------------|---|
| 8-34 | N NIII | СН | Н | HC1 | Colorless solid MS APCI(m/z): 356 [M+H]+ |
| 8-35 | H ₂ N NC NC | СН | Н | Free form | Colorless crystal Melting point: 181-184°C MS APCI(m/z): 218 [M+H]+ |
| 8-36 | H ₂ C | СН | Н | Free form | Slightly brownish oil MS APCI(m/z): 206 [M+H]+ |
| 8-37 | Nii | СН | н | 2HC1 | Pale brownish crystal Melting point: >300°C MS APCI(m/z): 169 |
| 8-38 | 38 O NIII- | СН | Н | 2HC1 | [M+H] Colorless powder MS APCI(m/z): 185 [M+H] |
| 8-39 | 39 | СН | H | 2HC1 | Colorless crystal Melting point: >300°C MS APCI(m/z): 217 [M+H] |
| 8-41 | 41 N S | СН | Н | Free form | Yellowish powder MS APCI(m/z): 234 [M+H]+ |
| 8-42 | 42 N | CH | H | Free form | Colorless powder MS·APCI(m/z): 217 [M+H]+ |
| 8-43 | 4'3 N | CH | Н | Free form | Colorless powder MS APCI(m/z): 228 [M+H]+ |
| 8-44 | 44 N | CH | Н | Free form | Colorless oil MS APCI (m/z): 244 [M+H]+ |
| 8-45 | 45 N~ | СН | Me | 2HC1 | Colorless resin MS-APCI(m/z): 183 [M+H]+ |
| | | | | | |

| Reference | | | Ι, | | Physical |
|----------------|------------------------------------|----|----------------|--------------|---|
| Example No. | R ² -X- | В | R ¹ | Salt | propertie etc. |
| 8-46 | CH ₁ | CH | Ме | 3HC1 | Colorless r MS APCI (m/z 248 [M+H]+ |
| 8-47 | H ₃ C N N~~ | СН | Ме | | |
| 8-48 | H2C_>-N_N~~ | СН | Ме | | 0 |
| 8-49 | H ₃ C CH ₃ | СН | Me | | |
| 8-50 | H,C N | СН | Ме | | |
| 8-51 | \$-O- | CH | Me | , | * * * |
| 8-52 | , O'-O | СН | Ме | | |
| 8-53 | | СН | Me | . • | * (* * * * * * * * * * * * * * * * * * |
| 8-54 | ~~~ | СН | Ме | 2HC1 | * |
| 8-55 | NC Nm. | CH | Me | Free form | Oil |
| 8-56 | H ₂ C-O | СН | Ме | Free form | Oil |
| 8-57 | H ₃ C Nillin | СН | Ме | Free form | Powder MS·APCI (m/z) 257 |
| 8-58 | H³C H³m. | СН | Ме | Free form | Purified pow MS-APCI(m/z) 271 |
| 8-59 | H ³ C \ CH ³ | CH | Me | Free form | Purified oil MS:APCI(m/z) |

Table 10

| * | R ² X- | -в | R ¹ | H ₂ | |
|-----------------------------|--------------------------------|-----|----------------|----------------|--|
| Reference Example No. | R²-x- | В | R ¹ | Salt | Physical properties, etc. |
| 9-1 | H,c^oll | . N | H | Free form | Colorless oil MS APCI (m/z): 285 |
| 9-2 | ° | N | н | Free form | Colorless oil MS APCI (m/z): 214 |
| 9-3 | H ₃ C ^{-N} | N | Н | Free form | Colorless oil MS APCI (m/z): 172 |
| 9-4 | | CH | H | form | |
| 9-5 | | CH | н | Free form | |
| 9-6 | H ₃ C O | CH | н | HC1 | |
| 9-7 | H ₃ C 0 | СН | Н | HC1 | |
| 9-8 | O | СН | н | Free form | Oil MS APCI(m/z): 268 |
| 9-9 | H ₃ C, Ollu. | СН | H | Free form | Oil MS APCI(m/z): 130 |
| 9-10 | H ₃ C Ohn. | CH | Н | Free form | Oil MS-APCI(m/z): 144 |
| 9-11 | H ₂ C Ollin | CH | Н | free | Oil MS·APCI(m/z): |

| | | EP 1 | 323 71 | IO A1 | |
|-----------------------------|------------------------|------|--------|--------------|--|
| | Tabl | e 10 | (Cor | ntinued |) ** *** |
| Reference Example No. | R ² -X- | В | Ri | Salt | Physical properties, etc. |
| 9-12 | H ² C O Om | СН | Н | Free | Oil MS APCI(m/z): 174 |
| 9-13 | H ₃ C Olin. | CH | Н | Free form | Oil MS APCI(m/z): 158 |
| 9-14 | NO IN | , CĤ | Н | Free | Yellowish crystal Melting point: 89-90°C |
| 9-15 | O ₂ N N O m | CH | Н | Free form | MS APCI (m/z): 252 Pale yellowish crystal Melting point: 133-134°C |
| 9-16 | (N) CN | СН | Н | Free form | MS APCI(m/z): 252 Colorless crystal Melting point: 64-65°C MS APCI(m/z): 232 |
| 9-17 | NC NO W | CH | Н | Free form | Colorless crystal Melting point: 124-126°C MS APCI(m/z): 232 |
| 9-18 | FINO | CH | Н | Free form | Yellowish crystal Melting point: 46-49°C MS APCI(m/z): 276 |
| 9-19 | N O MI | СН | Н | Free form | Colorless crystal Melting point: 57-59°C MS APCI(m/z): 208 |
| 9-20 | (N) CI | СН | н | Free form | Pale yellowish oil MS APCI(m/z): 242 and 244 |
| 9-21 | F CN | CH | Н | Free form | Pale yellowish crystal Melting point: 115-116°C |
| 9-22 | H ₃ C-O CN | CH | н | Free form | MS APCI(m/z): 249 Colorless crystal Melting point: 111-112°C MS APCI(m/z): 261 |
| 9-23 | CN CN | СН | Н | Free form | Colorless crystal Melting point: 121-122°C MS APCI(m/z): 265 |
| | Ċı . | | | | and 267 |

Table 10 (Continued)

| Reference Example No. | R²-X- | В | R¹ | Salt | Physical properties, etc. |
|-----------------------------|---------------------|----|----|--------------|--|
| 9-24 | H ₃ C CN | СН | H | Free form | Yellowish oil MS APCI(m/z): 245 |
| 9-25 | CN CN | СН | Н | Free form | Yellowish oil MS APCI(m/z): 231 |
| 9-26 | NC CO MILE | CH | Н | Free form | Yellowish oil MS APCI(m/z): 231 |
| 9-27 | O MO | CH | Н | Free form | Yellowish oil MS APCI(m/z): 251 |
| 9-28 | 03N | CH | Н | free form | Yellowish crystal Melting point: 86-87°C MS APCI(m/z): 251 |
| 9-29 | Br N O W. | СН | H | Free form | Colorless crystal Melting point: 126-127°C MS APCI(m/z): 286 and 288 |
| 9-30 | NC-S | CH | H | Free form | Colorless crystal Melting point: 325-326°C (decomposed) |
| 9-31 | O_2N $\sim S$ | CH | н | HC1 | Yellowish crystal Melting point: 328-329°C (decomposed) |
| 9-32 | F N | СН | Н | HC1 | Yellowish crystal Melting point: 292-294°C |
| 9-33 | CI—S | CH | Н | HC1 | Colorless crystal Melting point: 239-240°C |

Table 11

| | | | 47 | | | |
|------|-----------------------------|---------------------------------------|------|--------------------|-----------------|--|
| 5 | | | -х-в | O AMERICAN | NH ₂ | |
| 10 | Reference Example No. | R²-X- | В | R1 · | Salt | Physical properties, etc. |
| | 10-1 | O'N CONTUR | CH | н | Free form | Yellowish oil MS APCI(m/z): 319 [M+H]+ |
| 15 . | 10-2 | N N N | СН | н | 2HC1 | Colorless crystal Melting point: 250-253°C |
| 20 | 10-3 | CN H | СН | н | 2HC1 | Colorless crystal Melting point: >300°C MS APCI(m/z): 220 [M+H]+ |
| . 25 | 10-4 | S CH ₃ | СН | Н | 2HC1 | Colorless crystal Melting point: 277-278°C |
| 30 | 10-5 | C I'm | СН | Me | Free form | Colorless liquid MS APCI(m/z): 235 [M+H]+ |
| | 10-6 | | СН | Ме | Free form | Colorless crystal Melting point: 137-140°C |
| 35 | 10-7 | N N N | CH | Me | Free form | Colorless crystal Melting point: 126-128°C |
| 40 | 10-8 | | СН | Me | Free form | Colorless liquid MS-APCI(m/z): 234 [M+H]+ |
| | 10-9 | | CH | Me | Free form | Colorless liquid MS APCI(m/z): 234 [M+H]+ |
| 45 | 10-10 | | СН | Me | Free form | Colorless crystal Melting point: 97-99°C |
| 50 | 10-11 | N N N N N N N N N N N N N N N N N N N | СН | CH ₂ OH | 2HC1 | Colorless solid MS APCI(m/2): 250 [M+H]+ |

Table 11 (Continued)

| | | | , | 0 | | |
|----|-----------------------------|---|----|-------|---------------|---|
| 5 | Reference Example No. | R ² -X- | В | R1 · | Salt | Physical properties, etc. |
| 10 | 10-12 | N N N N N N N N N N N N N N N N N N N | СН | СН₂ОН | HC1 | Colorless solid MS APCI(m/z): 251 [M+H]+ |
| 15 | 10-13 | O ₂ N O H | СН | СН₂ОН | HC1 | Pale yellowish powder MS APCI(m/z): 284 [M+H]+ |
| | 10-14 | N CH, | СН | H | Free form | Colorless crystal Melting point: 60-62°C |
| 20 | 10-15 | CH ₃ | СН | Н | Free form | Colorless crystal Melting point: 73-75°C |
| 25 | 10-16 | N CH, | CH | Н | Free form | Colorless crystal Melting point: 82-83°C |
| 30 | 10-17 | ° N N CH3 | СН | Н | Free form | Colorless resin MS APCI(m/z): 270 [M+H]+ |
| 35 | 10-18 | H ² C — S — M _M , | CH | Н | Free form | Colorless crystal Melting point: 72-73°C |
| 40 | 10-19 | H ₃ C Q ₁ N ₁₁₁₁ CH ₃ | СН | H | .Free form | Colorless crystal Melting point: 91-94°C |
| 45 | 10-20 | CH, | CH | н | free form | Colorless crystal Melting point: 97-99°C |

Claims

1. An aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]:

$$R^2-X-B$$

$$NH-CH_2-CO-N$$

$$CN$$
[I]

wherein symbols in the formula have the following meanings;

A: -CH2- or -S-,

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B: CH or N.

R1: H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X: a single bonding arm, -CO-, -Alk-CO-, -COCH₂-, -Alk-O-, -O-CH₂-, -SO₂-, -S-, -COO-, -CON(\mathbb{R}^3)-, -Alk-CON(\mathbb{R}^3)-, -CON(\mathbb{R}^3)-, -Alk-CON(\mathbb{R}^3)-, -Alk-CO

where the bonding arm at a right terminus in each definition of the above X represents a bonding arm with B.

R3: hydrogen atom or a lower alky! group.

Alk: a lower alkylene group, and

R2: a group selected from the following (1), (2) and (3);

- (1) a cyclic group which may be substituted, where the cyclic group portion is
 - (i) a monocyclic or bicyclic hydrocarbon group, or
 - (ii) a monocyclic or bicyclic heterocyclic group:

(2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from a substituted or unsubstituted lower alkyl group; and

(3) a lower alkyl group, a carboxy lower alkyl group, a lower alkoxy group, a lower alkyl group, a carboxy lower alkyl group, a phenoxy group, a phenoxy-substituted lower alkyl group or a phenoxy group, a phenoxy-substituted lower alkyl group or a phenoxy lower alkenyl group.

- provided that when X is a single bonding arm, then R2 is a group selected from the above (1) and (2), and when X is -CO-, then B is N, or a pharmaceutically acceptable salt thereof.
 - 2. An aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I-e]:

wherein symbols in the formula have the following meanings;

A: -CH2- or -S-,

B: CH or N,

H1: H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X4: a single bonding arm, -Alk-CO-, -COCH₂-, -Alk-C-, -O-CH₂-, -SO₂-, -S., -COO-, -CON(R³)-, -Alk-CON (R³)-, -CON(R³)CH₂-, -Alk-CON(R³)CH₂-, -COCH₂N(R³)-, -SO₂N(R³)- or -NHCH₂-, -COCH₂N(R³)-, -CO

where the bonding arm at the right terminus in each definition of the above \underline{X} represents a bonding arm with B,

R3; hydrogen atom or a lower alkyl group.

Alk: a lower alkylene group,

R23: a group selected from the following (1) and (2);

- (1) a cyclic group which may be substituted, where the cyclic group portion is
 - (i) a monocyclic or bicyclic hydrocarbon group, or
 - (ii) a monocyclic or bicyclic heterocyclic group; and
- (2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from a substituted or unsubstituted lower alkyl group.

or a pharmaceutically acceptable salt thereof.

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- The compound according to Claim 1, wherein R² is a group selected from the following (1), (2) and (3);
 - (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the following substituents of Group A, where the cyclic group portion is
 - (i) a monocyclic or bicyclic hydrocarbon group, or
 - (ii) a monocyclic or bicyclic heterocyclic group:
 - (2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from "a lower alkyl group which may be substituted by substituent(s) selected from cyan group, a lower alkoxy group, phenyl group and a nitrogen-containing monocyclic 6-membered aromatic heterocyclic group"; and
 - (3) a lower alkyl group, a carboxy lower alkyl group, a lower alkoxy group, a lower alkenyl group, a lower alkoxy-substituted lower alkyl group, a phenoxy group, a phenoxy-substituted lower alkyl group or a phenyl lower alkonyl group.
 - Substituents of Group A: a halogen atom, cyano group, nitro group, amino group, oxo group, a lower alkoy group, a lower alkoy group, a lower alkoyson-bony a lower alkoyson-bony group, a lower alkoyson-bony and a lower cycloalkanoyl group, a halo-lower alkyl group, a halo-lower alkylca-bonyl group, a nitrogen-containing monocyclic 5- to 6-membered ariaphatic heterocyclic group, substituted carbonyl group, a monocyclic aryli group. a monocyclic aryli group, a monocyclic aryli group, a monocyclic aryli group, a monocyclic aryli group and an aminosulfonyl group.
 - The compound according to Claim 1, wherein R² is a cyclic group which may be substituted, where the cyclic group portion is a group selected from the following (i), (ii) and (iii);
- 40 (i) a monocyclic hydrocarbon group having 3 to 7 carbon atoms.
 - (ii) a monocyclic heterocyclic group containing 1 to 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and
 - (iii) a bicyclic heterocyclic group containing 1 to 3 hetero.atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused.
 - The compound according to Claim 4, wherein R² is a cyclic group which may have 1 to 3 substituents which are
 the same or different, where the cyclic group portion is a group selected from
 - pheny group, cyclohexyl group, cyclopentyl group, cyclopentyl group, cyclopenyl group, a pyrrollidinyl group, an oxolawyl group, a thiblanyl group, a pyrrollidinyl group, an imidazollidinyl group, an oxolawyl group, a thiblanyl group, a pyrrollid group, an imidazollidinyl group, an oxolawyl group, a pyrazollyl group, a triazolyl group, a triazolyl group, a thiblanyl group, an oxolawyl group, an oxolawyl group, an oxolawyl group, a material group, a morpholinyl group, a phenzilyl group, a morpholinyl group, a thiblanyl group, a pyridizinyl group, a pyridizinyl group, a pyridizinyl group, a pyridizinyl group, a morpholinyl group, an indiazolyl group, a pyridizinyl group, a pinyl group, an indiazolyl group, a morpholinyl group, a benzolinyl group, a thionopyridyl group, a group, a diazolinyl group, a thionopyridyl group, a quinoxallinyl group, a group, a morpholinyl group, a thionopyl group, a group, a quinoxallinyl group, a phibalazolyl group, a clumbolly group, a thionopyl group, a diverging a group, a diverging group, a diverging

group, a chromanyl group, an isochromanyl group, a naphthyridinyl group, and partially or completely saturated cyclic groups thereof.

6. The compound according to Claim 5, wherein R² is a cyclic group which may have substituents, where the cyclic group portion is a group selected from phenyl group, cycloheysl group, cyclopropyl group, a pyroblidinyl group, a middazolyl group, a pyracyl group, a middazolyl group, a pyracyl group, a pyracyl group, a middazolyl group, a pyracyl group, a gyracyl group, a gyracyl group, a gyracyl group, a gyracyl gyracy

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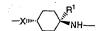
- The compound according to Claim 6, wherein R² is a cyclic group which may have substituents, where the cyclic group portion is a group selected from a piperickly group, a piperazinyl group, a morpholinyl group, an indolinyl group, an isolndolinyl group and a thiscolopyridyl group.
- 8. The compound according to any one of Claims 3 to 7, wherein R² is a cyclic group which may have 1 to 3 substituents, solected from the following substituents of Group A', where the cyclic group portion is a group solected from a piperickyl group, a piperazinyl group, a morpholinyl group, an indolinyl group, an isoindolinyl group and a thiszologyridyl group.

Substituents of Group A': oxo group, a lower alkanoyl group, a lower cycloalkanoyl group, a lower alkoxycarbonyl group and a nitrogen-containing aliphatic heterocyclic group-substituted carbonyl group.

9. The compound according to any one of Claims 2 to 8, wherein B is Cht, X is a single bonding arm and R² is (1) a monocyclic or bicyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group substituted by 1 or 2 substitutents selected from a substituted or unsubstituted lower alkyl group, represented by the formula:

- 35 10. The compound according to Claim 2, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group.
 - The compound according to Claim 3, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group.
 - The compound according to Claim 4, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group
- 13. The compound according to Claim 5, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group.
 - 14. The compound according to Claim 6, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group.
- 50 15. The compound according to Claim 7, wherein B is CH, X is a single bonding arm, A is -CH₂* and R¹ is hydrogen atom or a lower alkyl group.
 - The compound according to Claim 8, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group
 - 17. The compound according to Claim 9, wherein B is CH, X is a single bonding arm, A is -CH₂- and R¹ is hydrogen atom or a lower alkyl group.

- 18. The compound according to Claim 2, wherein B is CH, X is a single bonding arm, A is -S- and R1 is hydrogen atom or a lower alkyl group.
- The compound according to any one of Claims 1 to 18, wherein B is CH, and the compound has the following partial structure:



or a pharmaceutically acceptable salt thereof.

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- 15 20. A compound selected from the following group consisting of:
 - (S)-2-cyano-1-[t-4-(4-acetyl-1-piperazinyi)-1-methyl-r-1-cyclohexylaminolacetylpyrrolidine:
 - (S)-2-cyano-1-[trans-4-(1,3-dioxo-2-isoindolinyl)-cyclohexylamino]acetylpyrrolldine;
 - (S)-2-cyano-1-(trans-4-morpholinocyclohexylaminol-acotylpyrrolidine; and
 - (S)-2-cyano-1-[trans-4-(thiazolo[5,4-b]pyridin-2-yl)-cyclohexylamino]acetylpyrrolidine, or a pharmaceutically accordable salt thereof.
 - $\textbf{21.} \ \ A \, method \, for \, preparing \, an \, aliphatic \, nitrogen-containing \, \textbf{5}-membered \, ring \, compound \, represented by the \, formula \, [] \, ; \\$

 R^2-X-B $NH-CH_2-CO-N$ CN (1)

wherein symbols in the formula have the following meanings;

- A: -CH2- or -S-,
- B: CH or N,
- R1: H, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group.
- X: a. single bonding arm, -CO-, -Alk-CO-, -COCH₂-, -Alk-O-, -C-CH₂-, -SO₂-, -S-, -COO-, -CON(R³)-, -Alk-CON(R³)-, -COCH₂-, -CON(R³)-, -Alk-CON(R³)-, -COCH₂-, -COCH₂N(R³)-, or -NHCH₂-,
 - wherein the bonding arm at a right terminus in each definition of the above X represents a bonding arm with B.
 - R3: hydrogen atom or a lower alkyl group,
 - Alk: a lower alkylene group, and

R2: a group selected from the following (1), (2) and (3);

- (1) a cyclic group which may be substituted, where the cyclic group portion is
 - (i) a monocyclic or bicyclic hydrocarbon group, or
 - (ii) a monocyclic or bicyclic hydrocardon group;
- (2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from a substituted or unsubstituted lower alkyl group; and
- (3) a lower alkyl group, a carboxy lower alkyl group, a lower alkoxy group, a lower a kenyl group, a lower alkoy; substituted lower alkyl group, a phenoxy group, a phenoxy-substituted lower alkyl group or a phenyl lower alkenyl group, provided that when X is a single bonding arm, then R^o is a group selected from the above (1) and (2), and when X is -CO-, then B is N.

or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula [III]

$$Z^1$$
-CH₂-CO-N A [11]

wherein A represents -CH₂- or -S- and Z¹ represents a reactive residue, with a compound represented by the formula [III]:

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$$R^2$$
-X-B NH_2 [III]

wherein R1, R2, B and X have the same meanings as defined above, or salts thereof, and optionally making the product into a pharmaceutically acceptable sait thereof.

- 25 22. A method for inhibiting dipeptidy ipeptidase IV activity by using the compound according to any one of Claims 1 to 20.
 - 23. A method for treatment or prophylaxis of a disease, which comprises administering to a patient an effective dose of the compound according to any one of Claims 1 to 20.
- 30 24. The method for treatment or prophylaxis of a disease according to Claim 23, wherein the disease is expected to be alleviated by inhibiting dipeotidylpeotidase IV activity.
 - 25. The method for treatment or prophylaxis of a disease according to Claim 23, wherein the disease is diabetes
 - 26. The method for treatment or prophylaxis of a disease according to Claim 23, wherein the disease is type 2 diabetes.
 - 27. Use of the compound according to any one of Claims 1 to 20 as an inhibitor of dipeptidylpeptidase IV.
- 28. Use of the compound according to any one of Claims 1 to 20 as a pharmaceutically effective ingredient of a medlcine.
 - 29. Use of the compound according to any one of Claims 1 to 20 for the preparation of a medicine.
- 30. The use according to Claim 23 or 24, wherein the medicine is for the treatment or prophylaxis of a disease that is expected to be improved by inhibiting dipeptidylpeptidase IV activity.
 - 31. The use according to Claim 28 or 29, wherein the medicine is for the treatment or prophylaxis of diabetes.
- 32. The use according to Claim 28 or 29, wherein the medicine is for the treatment or prophylaxis of type 2 diabetes.
- A pharmaceutical composition comprising the compound according to any one of Claims 1 to 20 as an effective ingredient.
- The pharmacoutical composition according to Claim 33 wherein the pharmacoutical composition is a dipoptidylpectidase IV inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.

| | | | PCT/J | P01/08802 | | | |
|---|--|---|--|--|--|--|--|
| Int: 401/ 31/4 According 1 | CLASSFICATION OF SUBJECT MATTER Int. Cl. 2 (OTDRO7)16, 401/14, 403/12, 403/14, 471/04, 513/04, 413/12, 413/14, 403/12, 405/12, 417/12, 409/14, 417/14, A61K31/437, 31/456, 31/506, 31/4545, 31/497, 31/501, 31/4035, According to International Placer Classification (IPC) on to both pational classification and IPC FIELDS SEARCISED | | | | | | |
| Minimum d Int. 401/ 31/4 | B. FILLON SEASCHULDS. Minimum documentation seasoned (close) filestion system followed by closuffiction symbols Int. C1 ² CO70207/16, 401/14, 403/12, 403/4, 473/04, 513/04, 413/12, 413/14 401/12, 405/12, 417/12, 409/14, 417/24, A03K31/437, 31/454, 31/506, 31/4545 31/497, 31/501, 31/4035, | | | | | | |
| Documentet | ion searched other than minimum documentation to th | e extent that such docu | ments are included | in the fields searched | | | |
| | ate bose consulted during the international search (name in the consulted during the international search (name in the consultation), REGISTRY (STN), WPTDS (STN) | ne of data hase and, wh | ere practicable, se | rch lerms used) | | | |
| C. DOCU | MENTS CONSIDERED TO BE RELEVANT | | | | | | |
| Calegory | Citation of document, with indication, where a | propriete, of the releva | nt passages | Relevant to claim No. | | | |
| A | US 6110949 A (Novertis AG), 28 August 2000 (29.08.00), the whole document (Family: none) | | | | | | |
| λ | US 6013155 A (Movertis Ad), 04 January, 2000 (04.01.00), the whole document & US 6124305 A | | | 1-21,29-34 | | | |
| _ | documents are listed in the continuation of Box C. | See patent fami | • | | | | |
| "L" docume conside date date docume cited to special docume means docume than the Date of the a | cotagories of ofted desumentar to confidence in a confidence of the confidence of th | priority date and understand the pin "X" document of particular considered novel step when the document of particular considered to inva combined with on combination bein; "&" document membe | not in conflict with at inclpic or theory under or council to conside constant is taken alone cultur relevance; the coller relevance; the solve an inventive step or more other such g obvious to a person of the same patent! | laismed invention cannot be ed to favolve an inventive datimed invention cannot be when the document is documents, such skilled in the art omity | | | |
| | ailing address of the ISA/ nesse Patent Office | Authorized officer | | | | | |
| Facsimile No | 5 . | Telephone No. | | | | | |

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No. PCT/JP01/08802

| Box 1 Observations where certain claims were found unsearchable (Continuation of tiem 1 of first sheet) |
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| This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: |
| |
| 1. Claims Nos.: 22-28 |
| because they relate to subject matter not required to be searched by this Authority, namely: |
| Claims 22-28 relate to methods for treatment of the human body by therapy. |
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| - |
| 2 1 Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an |
| extent that no meaningful international search one be carried out, specifically: |
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| 3. Claims Nos.: |
| because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a). |
| Box II Observations where unity of invention is lacking (Continuation of liem 2 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: |
| This trace industrial deal of high Admittaly Toucha manapire investions in this international application, as sonows; |
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| 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable |
| clains. |
| 2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment |
| of any additional fee, |
| 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers |
| only those claims for which fees were paid, specifically claims Nos.: |
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| 4. No required additional search fees were timely paid by the applicant. Consequently, this international |
| search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: |
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| |
| Remark on Protest The additional search fees were accompanied by the applicant's protest. |
| No protest accompanied the payment of additional search fees. |
| |

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/08802

| Continuation of A. 21/401,33/4439,31/4178,31/4025,31/5377,31/496,31/4709,31/427,31/422,31/423,31/426,31/4709,31/427,31/422,31/423,31/426,31/42 | , |
|--|---|
| Continuation of B. | |
| 31/401,31/4439,31/4178,31/4025,31/5377,31/496,31/4709,31/427,31/422,31/423,31/426,31/517 | |
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